

US011421284B2

(12) **United States Patent**
Knudsen

(10) **Patent No.:** **US 11,421,284 B2**
(45) **Date of Patent:** ***Aug. 23, 2022**

(54) **METHODS FOR PREDICTING DRUG RESPONSIVENESS IN CANCER PATIENTS**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **16/927,725**

(22) Filed: **Jul. 13, 2020**

(65) **Prior Publication Data**

US 2020/0340067 A1 Oct. 29, 2020

Related U.S. Application Data

(63) Continuation of application No. 15/647,464, filed on Jul. 12, 2017, now abandoned, which is a continuation of application No. 15/289,026, filed on Oct. 7, 2016, now Pat. No. 9,725,769.

(51) **Int. Cl.**

C12Q 1/68 (2018.01)
C12Q 1/6886 (2018.01)
A61K 31/122 (2006.01)
A61K 45/06 (2006.01)
A61K 9/00 (2006.01)

(52) **U.S. Cl.**

CPC **C12Q 1/6886** (2013.01); **A61K 9/0019** (2013.01); **A61K 31/122** (2013.01); **A61K 45/06** (2013.01); **C12Q 2600/106** (2013.01); **C12Q 2600/158** (2013.01)

(58) **Field of Classification Search**

CPC C12Q 1/68
USPC 435/6.1
See application file for complete search history.

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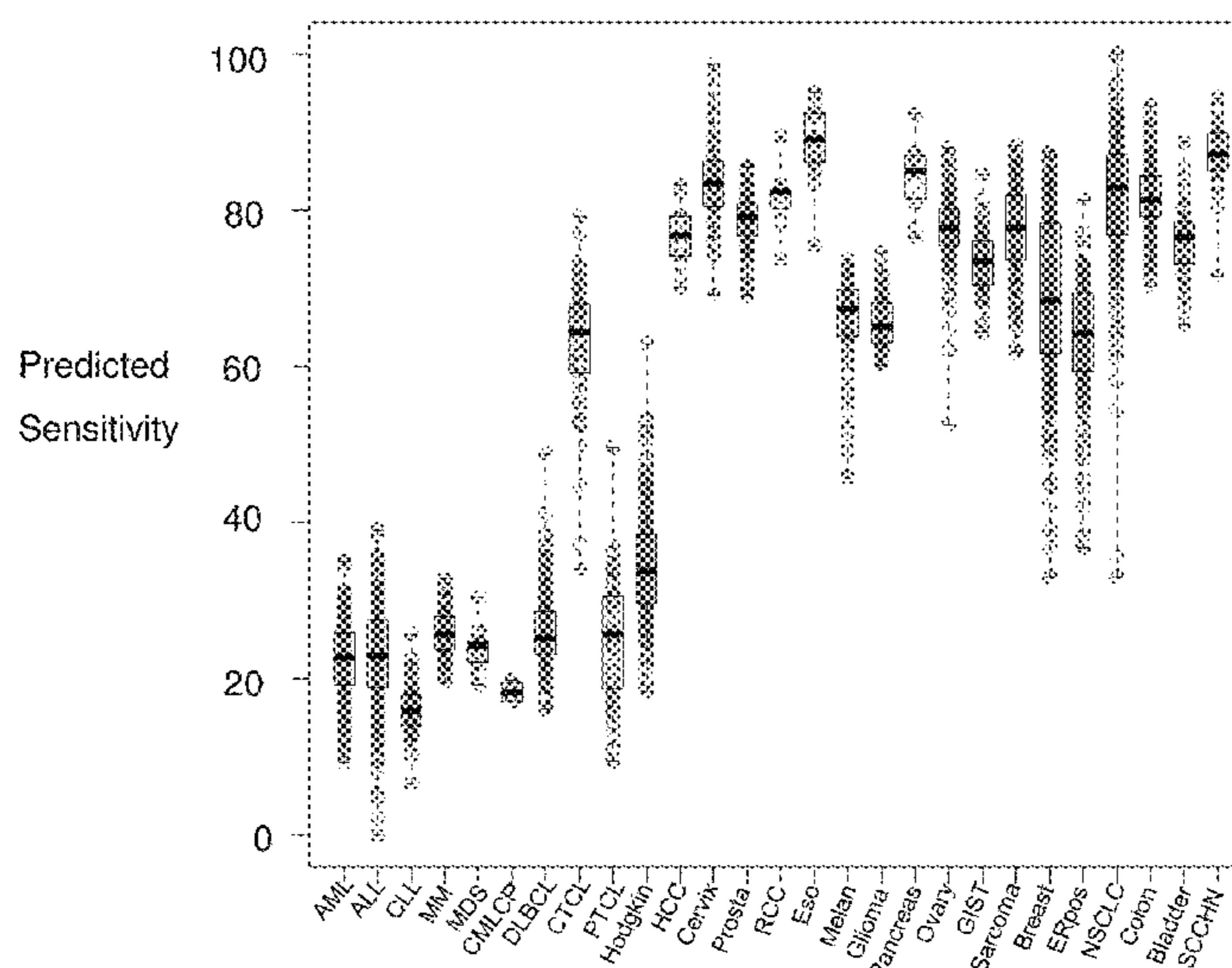
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(57) **ABSTRACT**

The present invention features methods, devices, and kits for detecting expression in a patient having cancer or determining responsive of a patient having cancer to a treatment, such as irofulven. The invention further includes methods of treating a patient having cancer by administering, e.g., irofulven.

20 Claims, 1 Drawing Sheet

Specification includes a Sequence Listing.



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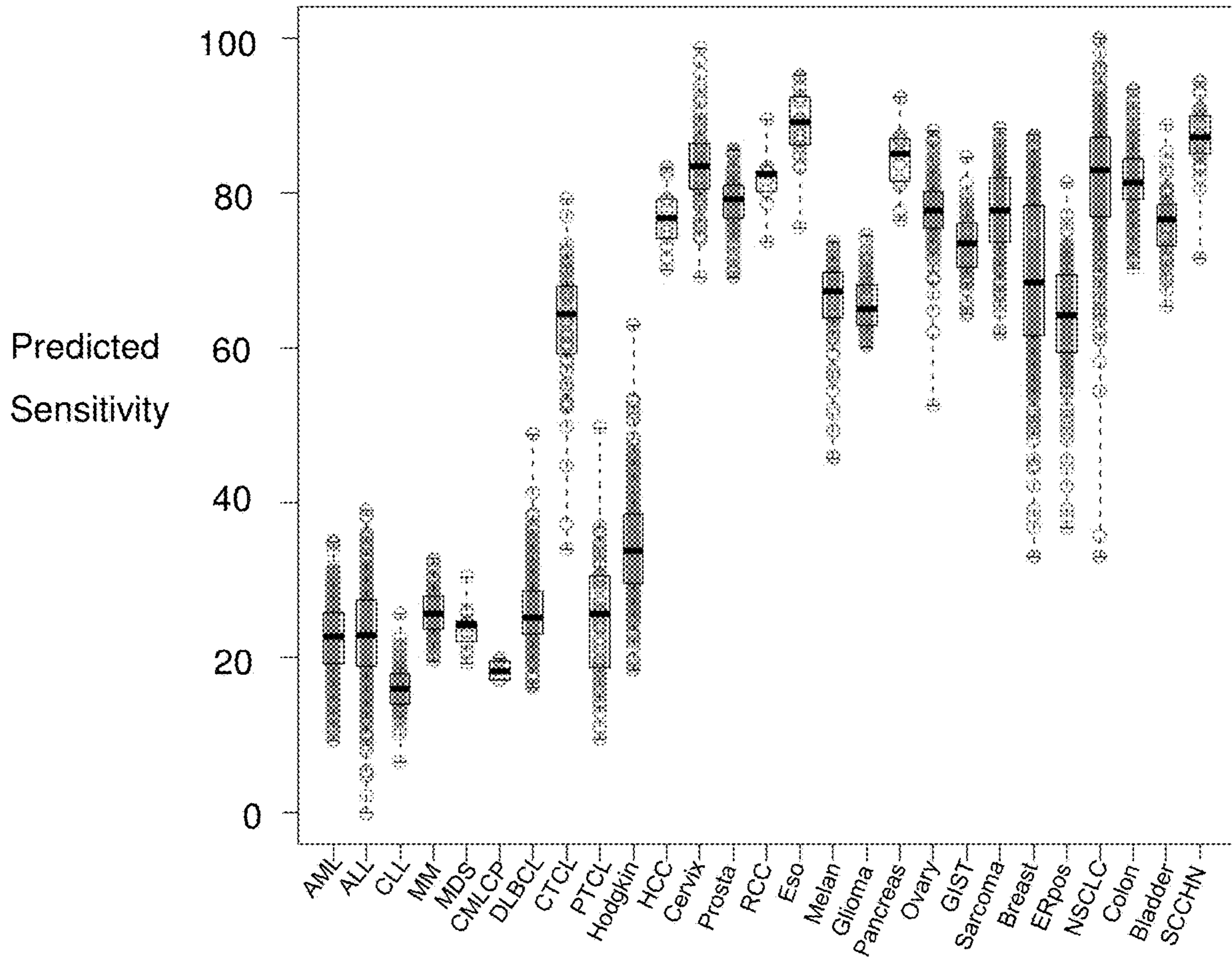
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**METHODS FOR PREDICTING DRUG
RESPONSIVENESS IN CANCER PATIENTS**

FIELD OF THE INVENTION

The invention features methods to detect the expression levels of genes encoding biomarkers in cancer patients and to predict the responsiveness of cancer patients to irifolven.

BACKGROUND

DNA microarrays have been used to measure gene expression in samples from patients and to facilitate diagnosis of disease. Gene expression can reveal the presence of cancer in a patient in addition to the type, stage, and origin of the cancer. Gene expression may even have a role in predicting the efficacy of cancer therapies. In recent decades, the National Cancer Institute (NCI) has tested cancer therapeutics for their effect in limiting the growth of 60 human cancer cell lines. The NCI has also measured gene expression in those 60 cancer cell lines using DNA microarrays. Various studies have explored the relationship between gene expression and therapeutic effect using the NCI datasets.

During cancer treatment, critical time is often lost due to a trial and error approach to finding an effective therapy. In addition, cancer cells often develop resistance to a previously effective therapy. In such situations, patient outcome would be greatly improved by early detection of such resistance.

Thus, there exists a need in the art for methods and devices that can predict the responsiveness of cancer patients to a medical treatment.

SUMMARY OF THE INVENTION

The invention features methods for detecting expression of a biomarker (e.g., one, two, three, four, five, ten, twenty, or all of the biomarkers shown in Tables 1-4, such as ATP1B1 (SEQ ID NO: 201)) in a patient having cancer, such as a patient having cancer (e.g., a human) that is resistant to one or more cancer therapies other than irifolven (e.g., a patient with prostate cancer, ovarian cancer, or hepatocellular carcinoma (HCC) that is resistant to one or more cancer therapies other than irifolven), and for determining responsiveness of a cancer patient (e.g., a patient with prostate cancer, ovarian cancer, or HCC) to treatment with irifolven. The invention also features methods of treating cancer in a patient in need thereof (e.g., a patient with prostate cancer, ovarian cancer, or HCC or a treatment resistant form thereof) that include administering irifolven to the patient, in which the patient is or has been determined to be responsive to irifolven according to the diagnostic methods described herein.

Exemplary types of cancer that can be diagnosed or treated with the methods include, e.g., prostate cancer, ovarian cancer (e.g., ovarian adenocarcinoma or embryonal carcinoma), liver cancer (e.g., HCC or hepatoma), myeloma (e.g., multiple myeloma), colorectal cancer (e.g., colon cancer and rectal cancer), leukemia (e.g., acute myeloid leukemia, acute lymphoid leukemia, chronic myeloid leukemia, chronic lymphocytic leukemia, acute myeloblastic leukemia, acute promyelocytic leukemia, acute myelomonocytic leukemia, acute monocytic leukemia, acute erythroleukemia, and chronic leukemia), myelodysplastic syndrome, lymphoma (e.g., diffuse large B-cell lymphoma, cutaneous T-cell lymphoma, peripheral T-cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, Walden-

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strom's macroglobulinemia, and lymphocytic lymphoma), cervical cancer, esophageal cancer, melanoma, glioma (e.g., oligodendroglioma), pancreatic cancer (e.g., adenocarcinoma, signet ring cell carcinoma, hepatoid carcinoma, colloid carcinoma, islet cell carcinoma, and pancreatic neuroendocrine carcinoma), gastrointestinal stromal tumor, sarcoma (e.g., fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, leiomyosarcoma, Ewing's sarcoma, and rhabdomyosarcoma), breast cancer (e.g., medullary carcinoma), ER-positive cancer, bladder cancer, head and neck cancer (e.g., squamous cell carcinoma of the head and neck), lung cancer (e.g., non-small cell lung carcinoma, large cell carcinoma, bronchogenic carcinoma, and papillary adenocarcinoma), metastatic cancer, oral cavity cancer, uterine cancer, testicular cancer (e.g., seminoma and embryonal carcinoma), skin cancer (e.g., squamous cell carcinoma, and basal cell carcinoma), thyroid cancer (e.g., papillary carcinoma and medullary carcinoma), brain cancer (e.g., astrocytoma and craniopharyngioma), stomach cancer, intraepithelial cancer, bone cancer, biliary tract cancer, eye cancer, larynx cancer, kidney cancer (e.g., renal cell carcinoma and Wilms tumor), gastric cancer, blastoma (e.g., nephroblastoma, medulloblastoma, hemangioblastoma, neuroblastoma, and retinoblastoma), polycythemia vera, chordoma, synovioma, mesothelioma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, cystadenocarcinoma, bile duct carcinoma, choriocarcinoma, epithelial carcinoma, ependymoma, pinealoma, acoustic neuroma, schwannoma, meningioma, pituitary adenoma, nerve sheath tumor, cancer of the small intestine, cancer of the endocrine system, cancer of the penis, cancer of the urethra, cutaneous or intraocular melanoma, a gynecologic tumor, solid tumors of childhood, or neoplasms of the central nervous system. For example, the cancer may be a solid tumor or a hematological cancer.

A first aspect of the invention features a method for detecting expression of a biomarker (e.g., one, two, three, four, five, ten, twenty, or all of the biomarkers shown in Tables 1 and/or 2, such as ATP1B1 (SEQ ID NO: 201)) in a patient having cancer (e.g., prostate cancer, ovarian cancer, or HCC), such as a patient having cancer that is resistant to one or more cancer therapies other than irifolven (e.g., a patient with prostate cancer, ovarian cancer, or HCC that is resistant to one or more cancer therapies other than irifolven). The method includes (a) contacting a sample (e.g., a tumor sample) from the patient including one or more nucleic acid molecules with a device (e.g., a microarray) including: i) one or more single-stranded nucleic acid molecules capable of specifically hybridizing with the nucleotides of one or more biomarkers of sensitivity selected from the biomarkers of Tables 1 and 3 (e.g., ATP1B1 (SEQ ID NO: 201)); and/or ii) one or more single-stranded nucleic acid molecules capable of specifically hybridizing with the nucleotides of one or more biomarkers of resistance selected from the biomarkers of Tables 2 and 4 (e.g., IGLC1 (SEQ ID NO: 301, 302, 303, or 318)); and (b) detecting a level of expression of one or more of the biomarker(s) of sensitivity and/or one or more of the biomarkers of resistance by performing microarray analysis or quantitative reverse transcriptase polymerase chain reaction (qRT-PCR). Expression of the biomarker(s) may be detected by determining the level of a messenger RNA (mRNA) transcribed from a nucleic acid molecule corresponding to a gene of the bio-

marker (s; e.g., a mRNA expressed from the ATP1B1 gene (SEQ ID NO: 201)) or a complementary DNA (cDNA) thereof.

A second aspect of the invention features a method of determining responsiveness of a patient having cancer (e.g., one of the cancers noted above, such as prostate cancer, ovarian cancer, or HCC) to irifolven. In particular, the patient may have a cancer that is resistant to one or more cancer therapies other than irifolven, such as prostate cancer, ovarian cancer, or HCC that is resistant to one or more cancer therapies other than irifolven. The method includes a) contacting a sample (e.g., a tumor sample) from the patient including one or more nucleic acid molecules with a device (e.g., a microarray or a device for performing a qRT-PCR reaction) including: i) one or more single-stranded nucleic acid molecules capable of specifically hybridizing with the nucleotides of one or more biomarkers of sensitivity selected from the biomarkers of Tables 1 and 3 (e.g., ATP1B1 (SEQ ID NO: 201)); and/or ii) one or more single-stranded nucleic acid molecules capable of specifically hybridizing with the nucleotides of one or more biomarkers of resistance selected from the biomarkers of Tables 2 and 4 (e.g., IGLC1 (SEQ ID NO: 301, 302, 303, or 318)); and b) measuring hybridization, or an amplification product resulting from hybridization, between the one or more nucleic acid molecules from the patient and the single-stranded nucleic acid molecules of the device to detect a level of expression of one or more of the biomarkers of sensitivity and/or one or more of the biomarkers of resistance. The patient is determined to be responsive to irifolven if: i) the level of expression of the biomarkers of sensitivity is substantially similar to the level of expression of the biomarkers of sensitivity (e.g., ATP1B1 (SEQ ID NO: 201)) in a cell (e.g., a cancer cell) or tissue (e.g., a tumor tissue) known to be sensitive to irifolven; and/or ii) the level of expression of the biomarkers of resistance (e.g., IGLC1 (SEQ ID NO: 301, 302, 303, or 318)) is substantially dissimilar to the level of expression of the biomarkers of resistance in a cell (e.g., a cancer cell) or tissue (e.g., a tumor tissue) known to be resistant to irifolven.

The method of the second aspect can further include administering irifolven to the patient if: i) the level of expression of the biomarkers of sensitivity (e.g., ATP1B1 (SEQ ID NO: 201)) is substantially similar to the level of expression of the biomarkers of sensitivity in a cell (e.g., a cancer cell) or tissue (e.g., a tumor tissue) known to be sensitive to irifolven; and/or ii) the level of expression of the biomarkers of resistance (e.g., IGLC1 (SEQ ID NO: 301, 302, 303, OR 318)) is substantially dissimilar to the level of expression of the biomarkers of resistance in a cell (e.g., a cancer cell) or tissue (e.g., a tumor tissue) known to be resistant to irifolven. The method can further include administering one or more cancer therapies other than irifolven to the patient if: i) the level of expression of the biomarkers of sensitivity (e.g., ATP1B1 (SEQ ID NO: 201)) is substantially dissimilar to the level of expression of the biomarkers of sensitivity in a cell (e.g., a cancer cell) or tissue (e.g., a tumor tissue) known to be sensitive to irifolven; and/or ii) the level of expression of the biomarkers of resistance is substantially similar to the level of expression of the biomarkers of resistance (e.g., IGLC1 (SEQ ID NO: 301, 302, 303, OR 318)) in a cell (e.g., a cancer cell) or tissue (e.g., a tumor tissue) known to be resistant to irifolven. In particular, the one or more of the cancer therapies includes surgery, radiation, or a therapeutic agent, such as a docetaxel, cabazitaxel, mitoxantrone, estramustine, prednisone, carboplatin, bevacizumab, paclitaxel, gemcitabine,

doxorubicin, topotecan, etoposide, tamoxifen, letrozole, sorafenib, fluorouracil, capecitabine, oxaliplatin, interferon-alpha, 5-fluorouracil (5-FU), a histone deacetylase (HDAC) inhibitor, ipilimumab, bortezomib, carfilzomib, thalidomide, lenalidomide, pomalidomide, dexamethasone, cyclophosphamide, vincristine, melphalan, tegafur, irinotecan, cetuximab, leucovorin, SN-38, everolimus, temsirolimus, bleomycin, lomustine, depsipeptide, erlotinib, cisplatin, busulfan, epirubicin, arsenic trioxide, bendamustine, fulvestrant, teniposide, adriamycin, decitabine, estramustine, azaguanine, aclarubicin, mitomycin, paclitaxel, taxotere, APO010, ara-c, methylprednisolone, methotrexate, methylgag, belinostat, idarubicin, IL4-PR38, valproic acid, all-trans retinoic acid (ATRA), cytoxan, suberoylanilide hydroxamic acid, leukeran, fludarabine, vinblastine, dacarbazine, hydroxyurea, tegafur, daunorubicin, mechlorethamine, streptozocin, carmustine, mercaptopurine, dactinomycin, tretinoin, ifosfamide, floxuridine, thioguanine, PSC 833, herceptin, celecoxib, iressa, anastrozole, and rituximab.

The invention also features a method of treating cancer in a patient in need thereof (e.g., one of the cancers noted above, such as prostate cancer, ovarian cancer, or HCC) that includes administering irifolven to the patient, in which the patient has been determined to be responsive to irifolven according to the method of the first or second aspect of the invention. In particular, the patient may have a cancer that is resistant to one or more cancer therapies other than irifolven (e.g., a patient with prostate cancer, ovarian cancer, or HCC that is resistant to one or more cancer therapies other than irifolven).

A third aspect of the invention features a method of treating a patient having cancer (e.g., one of the cancers noted above, such as prostate cancer, ovarian cancer, or HCC). In particular, the patient may have a cancer that is resistant to one or more cancer therapies other than irifolven (e.g., a patient with prostate cancer, ovarian cancer, or HCC that is resistant to one or more cancer therapies other than irifolven). The method includes a) contacting a sample (e.g., a tumor sample) from the patient including one or more nucleic acid molecules with a device (e.g., a microarray or a device for performing a qRT-PCR reaction) including: i) one or more single-stranded nucleic acid molecules capable of specifically hybridizing with the nucleotides of one or more biomarkers of sensitivity selected from the biomarkers of Tables 1 and 3 (e.g., ATP1B1 (SEQ ID NO: 201)); and/or ii) one or more single-stranded nucleic acid molecules capable of specifically hybridizing with the nucleotides of one or more biomarkers of resistance selected from the biomarkers of Tables 2 and 4 (e.g., IGLC1 (SEQ ID NO: 301, 302, 303, OR 318)); and b) measuring hybridization, or an amplification product resulting from hybridization, between the one or more nucleic acid molecules from the patient and the single-stranded nucleic acid molecules of the device to detect a level of expression of one or more of the biomarkers of sensitivity and/or one or more of the biomarkers of resistance; and c) administering irifolven to the patient if: i) the level of expression of the biomarkers of sensitivity is substantially similar to the level of expression of the biomarkers of sensitivity in a cell (e.g., a cancer cell) or tissue (e.g., a tumor tissue) known to be sensitive to irifolven; and/or ii) the level of expression of the biomarkers of resistance is substantially dissimilar to the level of expression of the biomarkers of resistance in a cell (e.g., a cancer cell) or tissue (e.g., a tumor tissue) known to be resistant to irifolven.

The method of the third aspect of the invention may further include administering one or more additional thera-

pies (e.g., surgery, radiation, or a therapeutic agent) to the patient prior to, concurrently with, or after administration of irifolven. In particular, the therapeutic agent may be selected from the group consisting of docetaxel, cabazitaxel, mitoxantrone, estramustine, prednisone, carboplatin, bevacizumab, paclitaxel, gemcitabine, doxorubicin, topotecan, etoposide, tamoxifen, letrozole, sorafenib, fluorouracil, capecitabine, oxaliplatin, interferon-alpha, 5-fluorouracil (5-FU), a histone deacetylase (HDAC) inhibitor, ipilimumab, bortezomib, carfilzomib, thalidomide, lenalidomide, pomalidomide, dexamethasone, cyclophosphamide, vincristine, melphalan, tegafur, irinotecan, cetuximab, leucovorin, SN-38, everolimus, temsirolimus, bleomycin, lomustine, depsipeptide, erlotinib, cisplatin, busulfan, epirubicin, arsenic trioxide, bendamustine, fulvestrant, teniposide, adriamycin, decitabine, estramustine, azaguanine, aclarubicin, mitomycin, paclitaxel, taxotere, APO010, ara-c, methylprednisolone, methotrexate, methyl-gag, belinostat, idarubicin, IL4-PR38, valproic acid, all-trans retinoic acid (ATRA), cytoxan, suberoylanilide hydroxamic acid, leukeran, fludarabine, vinblastine, dacarbazine, hydroxyurea, tegafur, daunorubicin, mechlorethamine, streptozocin, carmustine, mercaptopurine, dactinomycin, tretinoin, ifosfamide, floxuridine, thioguanine, PSC 833, herceptin, celecoxib, iressa, anastrozole, and rituximab. The therapeutic agent can be administered parenterally (e.g. intravenously, intramuscularly, transdermally, intradermally, intra-arterially, intracranially, subcutaneously, intraorbitally, intraventricularly, intraspinally, intraperitoneally, or intranasally), enterally, or topically.

In the second or third aspect of the invention, irifolven may be administered parenterally (e.g. intravenously, intramuscularly, transdermally, intradermally, intra-arterially, intracranially, subcutaneously, intraorbitally, intraventricularly, intraspinally, intraperitoneally, or intranasally), enterally, or topically. Preferably, irifolven is administered by intravenous injection. Irifolven may be administered to the patient two or more times, such as one or more times daily, weekly, every two weeks, every three weeks, or monthly (e.g., one or more times per week for two weeks or more). Additionally, a second dose of irifolven may be administered to the patient two weeks, three weeks, four weeks, or five weeks after administration of a prior dose of irifolven. In particular, irifolven is administered in a 3 week treatment regimen in which the irifolven is administered on day 1 and day 8. The treatment regimen may be repeated two to twenty times or more, as needed.

In particular, irifolven may be administered to the patient at a dose of about 0.05 mg/kg to 5 mg/kg, such as at a dose of about 0.1 mg/kg to 1 mg/kg. For example, irifolven may be administered at a dose of about 0.15 mg/kg, 0.20 mg/kg, 0.25 mg/kg, 0.30 mg/kg, 0.35 mg/kg, 0.40 mg/kg, 0.45 mg/kg, 0.55 mg/kg, 0.60 mg/kg, 0.65 mg/kg, 0.70 mg/kg, 0.75 mg/kg, 0.80 mg/kg, 0.85 mg/kg, 0.90 mg/kg, or 0.95 mg/kg. Irifolven may be administered to the patient in a treatment regimen at least once per week for at least two weeks and/or on day 1 and day 8 of a 3 week treatment regimen, in which the treatment regimen occurs one or more times (e.g., the treatment regimen is repeated two to twenty times). In particular, irifolven is administered to the patient at a dose of about 0.1 mg/kg to 1 mg/kg, such as a dose of about 0.2 mg/kg to about 0.6 mg/kg (e.g., a dose of about 0.45 mg/kg). This dosage of irifolven can be administered in a 3 week treatment regimen, in which irifolven is administered on day 1 and day 8.

In the second or third aspect of the invention, the contacting step (a) and the measuring step (b) may occur prior

to, concurrent with, or after administration of irifolven to the patient. Additionally, the contacting step (a) and the measuring step (b) may occur two or more times, e.g., during treatment with irifolven. For example, the contacting step (a) and the measuring step (b) may occur two or more times to assess the continued sensitivity of the patient to irifolven.

In any of the above aspects of the invention, the device can include at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, at least ten, or more single-stranded nucleic acid molecules capable of specifically hybridizing with the nucleotides of one or more biomarkers of sensitivity selected from the biomarkers of Tables 1 and 3 (e.g., ATP1B1 (SEQ ID NO: 201)); and/or at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, at least ten, or more single-stranded nucleic acid molecules capable of specifically hybridizing with the nucleotides of one or more biomarkers of resistance selected from the biomarkers of Tables 2 and 4 (e.g., IGLC1 (SEQ ID NO: 301, 302, 303, OR 318)). In particular, one or more of the single-stranded nucleic acid molecules of the device have a length in the range of 10 to 100 nucleotides in length (e.g., a length in the range of 20 to 60 nucleotides).

In any of the above aspects of the invention, the method may include converting the level of expression of one or more of the biomarkers of sensitivity (e.g., one, two, three, four, five, ten, twenty, or all of the biomarkers shown in Tables 1 and 3, such as ATP1B1 (SEQ ID NO: 201)) and/or one or more of the biomarkers of resistance (e.g., one, two, three, four, five, ten, twenty, or all of the biomarkers shown in Tables 2 and 4, such as IGLC1 (SEQ ID NO: 301, 302, 303, OR 318)) into a mean score, in which the mean score indicates the responsiveness of the patient to irifolven. The method can further include subtracting the mean score for one or more of the biomarkers of resistance (e.g., one, two, three, four, five, ten, twenty, or all of the biomarkers shown in Tables 2 and 4, such as IGLC1 (SEQ ID NO: 301, 302, 303, OR 318)) from the mean score for one or more of the biomarkers of sensitivity (e.g., one, two, three, four, five, ten, twenty, or all of the biomarkers shown in Tables 1 and 3, such as ATP1B1 (SEQ ID NO: 201)) to obtain a difference score, in which the difference score indicates the responsiveness of the patient to irifolven. In particular, the mean score and/or the difference score above a cutoff value indicates that the patient is responsive to irifolven, such as if the cutoff value is about 0.1, about 0.15, about 0.2, about 0.25, about 0.3, about 0.35, about 0.4, about 0.45, about 0.5, or greater.

In any of the above aspects of the invention, the biomarker of sensitivity may be selected from one or more of ATP1B1 (SEQ ID NO: 201 or 219), UCHL1 (SEQ ID NO: 202), PTGR1 (SEQ ID NO: 203 or 210), NME7 (SEQ ID NO: 204), PLS3 (SEQ ID NO: 205), S100A10 (SEQ ID NO: 206), CD24 (SEQ ID NO: 207, 209, or 220), NQO1 (SEQ ID NO: 208 or 216), MYOF (SEQ ID NO: 211), LAPTM4B (SEQ ID NO: 212), CALD1 (SEQ ID NO: 213), PDGFC (SEQ ID NO: 214), BASP1 (SEQ ID NO: 215), ID1 (SEQ ID NO: 217), and GJA1 (SEQ ID NO: 218). The biomarker of resistance may be selected from one or more of IGLC1 (SEQ ID NO: 301, 302, 303, or 318), LAPTM5 (SEQ ID NO: 304 or 338), ARHGDIB (SEQ ID NO: 305 or 311), SLC43A3 (SEQ ID NO: 307), LCP1 (SEQ ID NO: 308), HCLS1 (SEQ ID NO: 309), CD53 (SEQ ID NO: 310), MZB1 (SEQ ID NO: 313), RASSF5 (SEQ ID NO: 314 or 386), FAM46C (SEQ ID NO: 315), RCSD1 (SEQ ID NO: 316), IGJ (SEQ ID NO: 317), LPXN (SEQ ID NO: 319), ITGB7 (SEQ ID NO: 320), and GTSF1 (SEQ ID NO: 321).

RASSF5 (SEQ ID NO: 314 or 386), FAM46C (SEQ ID NO: 315), RCSD1 (SEQ ID NO: 316), IGJ (SEQ ID NO: 317), and LPXN (SEQ ID NO: 319). The biomarkers of resistance may include IGLC1 (SEQ ID NO: 301, 302, 303, or 318), LPTM5 (SEQ ID NO: 304 or 338), ARHGDIB (SEQ ID NO: 305 or 311), SLC43A3 (SEQ ID NO: 307), LCP1 (SEQ ID NO: 308), HCLS1 (SEQ ID NO: 309), CD53 (SEQ ID NO: 310), MZB1 (SEQ ID NO: 313), RASSF5 (SEQ ID NO: 314 or 386), FAM46C (SEQ ID NO: 315), RCSD1 (SEQ ID NO: 316), IGJ (SEQ ID NO: 317), LPXN (SEQ ID NO: 319), and ITGB7 (SEQ ID NO: 320). The biomarkers of resistance may include IGLC1 (SEQ ID NO: 301, 302, 303, or 318), LPTM5 (SEQ ID NO: 304 or 338), ARHGDIB (SEQ ID NO: 305 or 311), SLC43A3 (SEQ ID NO: 307), LCP1 (SEQ ID NO: 308), HCLS1 (SEQ ID NO: 309), CD53 (SEQ ID NO: 310), MZB1 (SEQ ID NO: 313), RASSF5 (SEQ ID NO: 314 or 386), FAM46C (SEQ ID NO: 315), RCSD1 (SEQ ID NO: 316), IGJ (SEQ ID NO: 317), LPXN (SEQ ID NO: 319), ITGB7 (SEQ ID NO: 320), and GTSF1 (SEQ ID NO: 321).

In any of the above aspects of the invention, the device can be a microarray, such as a deoxyribonucleic acid (DNA)-based platform. Alternatively, the device can be for performing a qRT-PCR reaction (e.g., the device is used with a system for detecting the amplification product, for example, by fluorescence or by another method). The methods may also utilize both a microarray and a qRT-PCR. Thus, the expression level of the biomarkers of sensitivity (e.g., one, two, three, four, five, ten, twenty, or all of the biomarkers shown in Tables 1 and 3, such as ATP1B1 (SEQ ID NO: 201)) and/or the biomarkers of resistance (e.g., one, two, three, four, five, ten, twenty, or all of the biomarkers shown in Tables 2 and 4, such as IGLC1 (SEQ ID NO: 301, 302, 303, OR 318)) can be measured using qRT-PCR. In particular, the level of expression of one or more of the biomarkers of sensitivity and/or one or more of the biomarkers of resistance is determined by detecting the level of mRNA transcribed from one or more genes encoding one or more of the biomarkers of Tables 1-4.

In any of the above aspects of the invention, the cancer is selected from a solid tumor cancer and a hematological cancer. For example, the cancer is prostate cancer, ovarian cancer, HCC, multiple myeloma, breast cancer, acute myelogenous leukemia (AML), acute lympho-blastic leukemia (ALL), chronic lymphocytic leukemia (CLL), myelodysplastic syndrome (MDS), chronic myelogenous leukemia-chronic phase (CMLCP), diffuse large B-cell lymphoma (DLBCL), cutaneous T-cell lymphoma (CTCL), peripheral T-cell lymphoma (PTCL), Hodgkin's lymphoma, cervical cancer, renal cell carcinoma (RCC), esophageal cancer, melanoma, glioma, pancreatic cancer, gastrointestinal stromal tumors (GIST), sarcoma, estrogen receptor-positive (ERpos) breast cancer, non-small cell lung carcinoma (NSCLC), colon cancer, bladder cancer, or squamous cell carcinoma of the head and neck (SCCHN). In particular, the cancer is prostate cancer, such as prostate cancer that is resistant to one or more cancer therapies other than irifolven. The cancer may also be ovarian cancer, such as ovarian cancer that is resistant to one or more cancer therapies other than irifolven. Alternatively, the cancer may be HCC, such as HCC that is resistant to one or more cancer therapies other than irifolven.

In any of the above aspects of the invention, the patient may exhibit cancer relapse (e.g., relapse of prostate cancer, ovarian cancer, or HCC), such as relapse after treatment with a therapeutic agent other than irifolven. In particular, the patient may exhibit cancer relapse prior to treatment with

irifolven. Alternatively, the patient may have not been administered a treatment for cancer.

Definitions

As used herein, "a" or "an" means "at least one" or "one or more" unless otherwise indicated. In addition, the singular forms "a", "an", and "the" include plural referents unless the context clearly dictates otherwise.

As used herein, "about" refers to an amount $\pm 10\%$ of the recited value.

By "biomarker" is meant a nucleic acid molecule (e.g., a mRNA or its complement, for example, a cDNA) or a protein encoded by the nucleic acid molecule present in, or from, a cell or tissue. The expression of the biomarker correlates to the responsiveness (e.g., sensitivity or resistance) of the cell or tissue (and thus, the patient in which the cell or tissue resides or the patient from which the cell or tissue was obtained) to a cancer treatment (e.g., irifolven). In particular, a biomarker of sensitivity is a nucleic acid molecule (e.g., a mRNA or its complement) expressed from any one of the genes shown in Tables 1 and 3, or the protein encoded by the nucleic acid molecule, and a biomarker of resistance is a nucleic acid molecule (e.g., a mRNA or its complement) expressed from any one of the genes shown in Tables 2 and 4, or the protein encoded by the nucleic acid molecule.

The terms "cancer" and "cancerous" refer to or describe the physiological condition in mammals (e.g., humans) that is typically characterized by unregulated cell proliferation. Examples of cancer include, but are not limited to, prostate cancer, ovarian cancer (e.g., ovarian adenocarcinoma or embryonal carcinoma), liver cancer (e.g., hepatocellular carcinoma (HCC) or hepatoma), myeloma (e.g., multiple myeloma), colorectal cancer (e.g., colon cancer and rectal cancer), leukemia (e.g., acute myeloid leukemia, acute lymphoid leukemia, chronic myeloid leukemia, chronic lymphocytic leukemia, acute myeloblastic leukemia, acute promyelocytic leukemia, acute myelomonocytic leukemia, acute monocytic leukemia, acute erythroleukemia, and chronic leukemia), myelodysplastic syndrome, lymphoma (e.g., diffuse large B-cell lymphoma, cutaneous T-cell lymphoma, peripheral T-cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, Waldenstrom's macroglobulinemia, and lymphocytic lymphoma), cervical cancer, esophageal cancer, melanoma, glioma (e.g., oligodendroglioma), pancreatic cancer (e.g., adenosquamous carcinoma, signet ring cell carcinoma, hepatoid carcinoma, colloid carcinoma, islet cell carcinoma, and pancreatic neuroendocrine carcinoma), gastrointestinal stromal tumor, sarcoma (e.g., fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, leiomyosarcoma, Ewing's sarcoma, and rhabdomyosarcoma), breast cancer (e.g., medullary carcinoma), ER-positive cancer, bladder cancer, head and neck cancer (e.g., squamous cell carcinoma of the head and neck), lung cancer (e.g., non-small cell lung carcinoma, large cell carcinoma, bronchogenic carcinoma, and papillary adenocarcinoma), metastatic cancer, oral cavity cancer, uterine cancer, testicular cancer (e.g., seminoma and embryonal carcinoma), skin cancer (e.g., squamous cell carcinoma and basal cell carcinoma), thyroid cancer (e.g., papillary carcinoma and medullary carcinoma), brain cancer (e.g., astrocytoma and craniopharyngioma), stomach cancer, intra-epithelial cancer, bone cancer, biliary tract cancer, eye cancer, larynx cancer, kidney cancer (e.g., renal cell carcinoma and Wilms tumor), gastric cancer, blastoma (e.g., nephroblastoma, medulloblastoma, hemangioblastoma, neuroblastoma, and retinoblas-

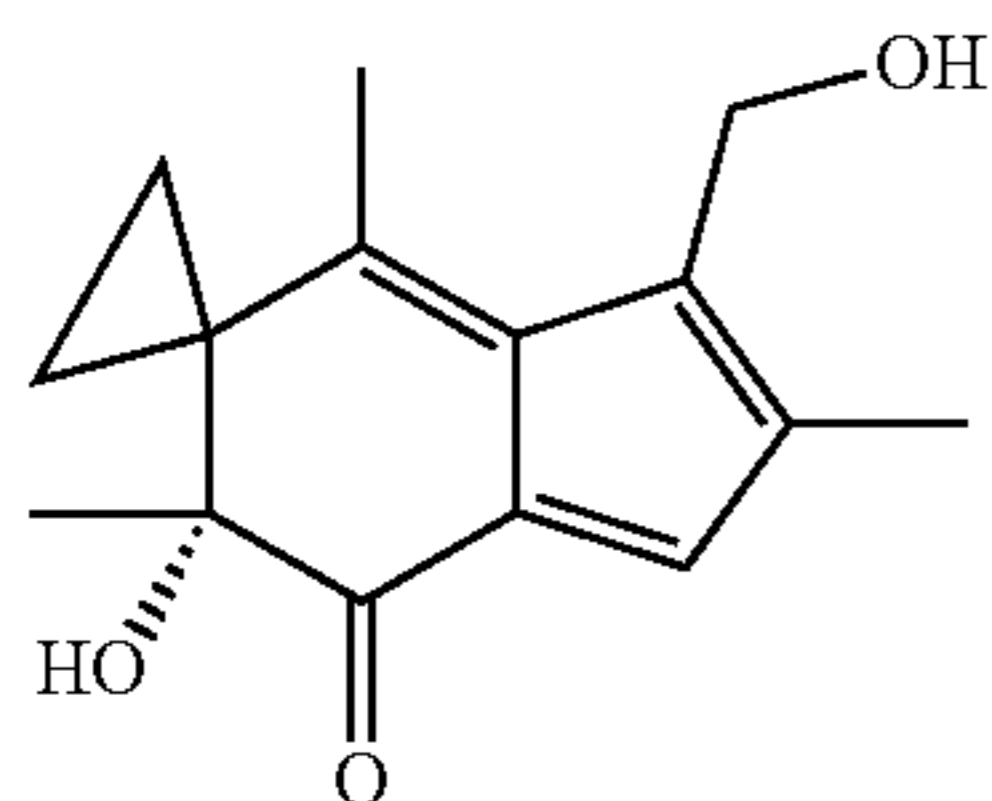
toma), polycythemia vera, chordoma, synovioma, mesothelioma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, cystadenocarcinoma, bile duct carcinoma, choriocarcinoma, epithelial carcinoma, ependymoma, pinealoma, acoustic neuroma, schwannoma, meningioma, pituitary adenoma, nerve sheath tumor, cancer of the small intestine, cancer of the endocrine system, cancer of the penis, cancer of the urethra, cutaneous or intraocular melanoma, a gynecologic tumor, solid tumors of childhood, and neoplasms of the central nervous system. The term cancer includes solid tumors (e.g., prostate cancer, ovarian cancer, or hepatocellular carcinoma (HCC)) and hematological cancers (e.g., cancer of the blood, such as lymphoma (e.g., cutaneous T-cell lymphoma (CTCL))).

The terms “expression level” and “level of expression,” as used herein, refer to the amount of a gene product in a cell, tissue, biological sample, organism, or patient, e.g., amounts of DNA, RNA (e.g. messenger RNA (mRNA)), or proteins corresponding to a given gene.

“Gene” as used herein indicates a coding or noncoding gene whose activity can be determined by measuring the produced RNA. Examples include protein coding genes, microRNAs, small nuclear RNAs and other RNAs with catalytic, regulatory or coding properties.

To “inhibit growth” as used herein means causing a reduction in cell growth (e.g., cancer cell growth, such as the NCI60 cancer cell lines) in vivo or in vitro by, e.g., 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or 99% or more, as evident by a reduction in the proliferation of cells exposed to a treatment (e.g., irifolven), relative to the proliferation of cells in the absence of the treatment. Growth inhibition may be the result of a treatment (e.g., irifolven) that induces apoptosis in a cell, induces necrosis in a cell, slows cell cycle progression, disrupts cellular metabolism, induces cell lysis, or induces some other mechanism that reduces the proliferation of cells.

The term “irifolven” as used herein refers to an antitumor agent that is a cytotoxic semi-synthetic derivative of illudin S, a sesquiterpene toxin found in the Jack ‘o’ Lantern mushroom. Irifolven or 6-hydroxymethylacylfulvene is an alkylating agent that initiates the apoptotic degradation of DNA leading to cell death. Irifolven ((6R)-6'-hydroxy-3'-(hydroxymethyl)-2',4',6'-trimethylspiro[cyclopropane-1,5'-inden]-7'(6'H)-one) has the structural molecular formula shown below:



Irifolven

Irifolven is also described in MacDonald et al. (*Cancer Res.* 57 (2): 279-283, 1997), hereby incorporated by reference.

“Microarray” as used herein means a device employed by any method that quantifies one or more subject oligonucleotides, e.g., RNA, DNA, cDNA, or analogues thereof, at a time. For example, many DNA microarrays, including those made by Affymetrix (e.g., an Affymetrix HG-U133A or HG-U133_Plus_2 array), use several probes for determining the expression of a single gene. The DNA microarray may contain oligonucleotide probes that may be, e.g., full-length

cDNAs complementary to an RNA or cDNA fragments that hybridize to part of an RNA. The DNA microarray may also contain modified versions of DNA or RNA, such as locked nucleic acids or LNA. Exemplary RNAs include mRNA, miRNA, and miRNA precursors.

As used herein, the term “percent (%) sequence identity” refers to the percentage of nucleic acid residues of a candidate sequence, e.g., a probe or primer of the invention, that are identical to the nucleic acid residues of a reference sequence, e.g., a biomarker sequence of the invention, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity (e.g., gaps can be introduced in one or both of the candidate and reference sequences for optimal alignment and non-homologous sequences can be disregarded for comparison purposes). Alignment for purposes of determining percent sequence identity can be achieved in various ways that are within the skill in the art, for instance, using computer software, such as BLAST, BLAST-2, BLAST-P, BLAST-N, BLAST-X, WU-BLAST-2, ALIGN, ALIGN-2, CLUSTAL, Megalign (DNASTAR). In addition, those skilled in the art can determine appropriate parameters for measuring alignment, including any algorithms needed to achieve optimal alignment over the length of the sequences being compared.

“NCI60” as used herein means a panel of 60 cancer cell lines from lung, colon, breast, ovarian, leukemia, renal, melanoma, prostate and brain cancers including the following cancer cell lines: NSCLC_NCIH23, NSCLC_NCIH522, NSCLC_A549ATCC, NSCLC_EK VX, NSCLC_NCIH226, NSCLC_NCIH332M, NSCLC_H460, NSCLC_HOP62, NSCLC_HOP92, COLON_HT29, COLON_HCC-2998, COLON_HCT116, COLON_SW620, COLON_COLO205, COLON_HCT15, COLON_KM12, BREAST_MCF7, BREAST_MCF7ADR, BREAST_MDAMB231, BREAST_HS578T, BREAST_MDAMB435, BREAST_MDN, BREAST_BT549, BREAST_T47D, OVAR_OVCAR3, OVAR_OVCAR4, OVAR_OVCAR5, OVAR_OVCAR8, OVAR_IGROV1, OVAR_SKOV3, LEUK_CCRFCM, LEUK_K562, LEUK_MOLT4, LEUK_HL60, LEUK_RPMI8266, LEUK_SR, RENAL_UO31, RENAL_SN12C, RENAL_A498, RENAL_CAKI1, RENAL_RXF393, RENAL_7860, RENAL_ACHN, RENAL_TK10, MELAN_LOXIMVI, MELAN_MALME3M, MELAN_SKMEL2, MELAN_SKMEL5, MELAN_SKMEL28, MELAN_M14, MELAN_UACC62, MELAN_UACC257, PROSTATE_PC3, PROSTATE_DUI45, CNS_SNB19, CNS_SNB75, CNS_U251, CNS_SF268, CNS_SF295, and CNS_SF539.

The terms “patient” and “subject,” as used interchangeably herein, refer to any animal (e.g., a mammal, such as a human). A patient to be treated or tested for responsiveness to a treatment (e.g., irifolven) according to the methods described herein may be one who has been diagnosed with a cancer, such as those described herein, e.g., prostate cancer, ovarian cancer, or hepatocellular carcinoma (HCC). Diagnosis may be performed by any method or techniques known in the art, such as x-ray, MRI, or biopsy, and confirmed by a physician. To minimize exposure of a patient to drug treatments that may not be therapeutic, the patient may be determined to be either responsive or non-responsive to a cancer treatment, such as irifolven, according to the methods described herein.

“Resistant” or “resistance” as used herein means that a cell (e.g., a cancer cell), a tissue (e.g., a tumor), or a patient having cancer (e.g., a human having cancer) is able to withstand treatment with an anti-cancer agent (e.g., irifolven). In particular, the treatment does not inhibit the growth

of a cancer cell in vitro by about 70%, 80%, 90%, 95%, 99% or 100% relative to the growth of a cancer cell not exposed to the treatment. Resistance to treatment may be determined by a cell proliferation assay, e.g., a cell-based assay, which

measures the growth of treated cells as a function of the absorbance of the cells of an incident light beam, such as the NCI60 assays described herein. In this assay, greater absorbance indicates greater cell growth, and thus, resistance to the treatment.

A cancer patient (e.g., a patient with prostate cancer, ovarian cancer, or a hepatocellular carcinoma) may also have resistance to a cancer therapy other than irifolven, such as surgery, radiation, or a therapeutic agent (e.g., docetaxel, cabazitaxel, mitoxantrone, estramustine, prednisone, carboplatin, bevacizumab, paclitaxel, gemcitabine, doxorubicin, topotecan, etoposide, tamoxifen, letrozole, sorafenib, fluorouracil, capecitabine, oxaliplatin, interferon-alpha, or 5-fluorouracil (5-FU)).

The terms “responsive” and “responsiveness,” as used herein, refer to the likelihood that a cancer treatment (e.g., irifolven) has (e.g., induces) a desired effect, or, alternatively, refer to the strength of a desired effect caused or induced by the treatment in a cell (e.g., a cancer cell), a tissue (e.g., a tumor), or a patient having cancer (e.g., a human having cancer). For example, the desired effect can include inhibition of the growth of a cancer cell in vitro by more than 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100% relative to the growth of a cancer cell not exposed to the treatment. The desired effect can also include reduction in tumor mass by, e.g., about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100%. Responsiveness to treatment may be determined by a cell proliferation assay, e.g., a cell-based assay, which measures the growth of treated cells as a function of the absorbance of the cells of an incident light beam, such as the NCI60 assays described herein. In this assay, lesser absorbance indicates lesser cell growth, and thus, sensitivity to the treatment. A greater reduction in growth indicates more sensitivity to the treatment. In particular, “responsiveness” is a measure of the sensitivity or resistance of a patient to a treatment for cancer (e.g., irifolven).

The term “sample,” as used herein, refers to any specimen (such as cells, tissue (e.g., a tissue sample obtained by biopsy), blood, serum, plasma, urine, cerebrospinal fluid, or pancreatic fluid) taken from a subject. Preferably, the sample is taken from a portion of the body affected by a cancer (e.g., a biopsy of the cancer tissue, such as prostate, ovarian, or lung cancer tissue). Biopsy may involve fine needle aspiration biopsy, core needle biopsy (e.g., stereotactic core needle biopsy, vacuum-assisted core biopsy, or magnetic resonance imaging (MRI) guided biopsy), or surgical biopsy (e.g., incisional biopsy or excisional biopsy). The sample may undergo additional purification and processing, for example, to remove cell debris and other unwanted molecules. Additional processing may further involve amplification, e.g., using PCR (RT-PCR). The standard methods of sample purification, such as removal of unwanted molecules, are known in the art.

“Sensitive” and “sensitivity” as used herein refer to a cell (e.g., a cancer cell), a tissue (e.g., a tumor), or a patient having cancer (e.g., a human having cancer) that is responsive to treatment, such as an anti-cancer agent (e.g., irifolven) or radiation treatment. In particular, the treatment inhibits the growth of a cancer cell in vitro by about 70%, 80%, 90%, 95%, 99% or 100% relative to the growth of a cancer cell not exposed to the treatment. Sensitivity to treatment may be determined by a cell proliferation assay,

e.g., a cell-based assay, which measures the growth of treated cells as a function of the absorbance of the cells of an incident light beam, such as the NCI60 assays described herein. In this assay, lesser absorbance indicates lesser cell growth, and thus, sensitivity to the treatment.

“Treatment,” “medical treatment,” to “treat,” and “therapy,” as used interchangeably herein, refer to administering or exposing a patient having cancer (e.g., a human), a cell, or a tumor to an anti-cancer agent (e.g., a drug, a protein, an antibody, a nucleic acid, a chemotherapeutic agent, or a radioactive agent), or to some other form of medical intervention used to treat or prevent a disease, disorder, or condition (e.g., surgery, cryotherapy, radiation therapy, or combinations thereof). In particular, a medical treatment can include irifolven. For example, the cancer to be treated is a solid tumor or a hematological cancer. Examples of cancer include, e.g., prostate cancer, ovarian cancer (e.g., ovarian adenocarcinoma or embryonal carcinoma), liver cancer (e.g., hepatocellular carcinoma (HCC) or hepatoma), myeloma (e.g., multiple myeloma), colorectal cancer (e.g., colon cancer and rectal cancer), leukemia (e.g., acute myeloid leukemia, acute lymphoid leukemia, chronic myeloid leukemia, chronic lymphocytic leukemia, acute myeloblastic leukemia, acute promyelocytic leukemia, acute myelomonocytic leukemia, acute monocytic leukemia, acute erythroleukemia, and chronic leukemia), myelodysplastic syndrome, lymphoma (e.g., diffuse large B-cell lymphoma, cutaneous T-cell lymphoma, peripheral T-cell lymphoma, Hodgkin’s lymphoma, non-Hodgkin’s lymphoma, Waldenström’s macroglobulinemia, and lymphocytic lymphoma), cervical cancer, esophageal cancer, melanoma, glioma (e.g., oligodendroglioma), pancreatic cancer (e.g., adenocarcinoma, signet ring cell carcinoma, hepatoid carcinoma, colloid carcinoma, islet cell carcinoma, and pancreatic neuroendocrine carcinoma), gastrointestinal stromal tumor, sarcoma (e.g., fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, leiomyosarcoma, Ewing’s sarcoma, and rhabdomyosarcoma), breast cancer (e.g., medullary carcinoma), ER-positive cancer, bladder cancer, head and neck cancer (e.g., squamous cell carcinoma of the head and neck), lung cancer (e.g., non-small cell lung carcinoma, large cell carcinoma, bronchogenic carcinoma, and papillary adenocarcinoma), metastatic cancer, oral cavity cancer, uterine cancer, testicular cancer (e.g., seminoma and embryonal carcinoma), skin cancer (e.g., squamous cell carcinoma and basal cell carcinoma), thyroid cancer (e.g., papillary carcinoma and medullary carcinoma), brain cancer (e.g., astrocytoma and craniopharyngioma), stomach cancer, intraepithelial cancer, bone cancer, biliary tract cancer, eye cancer, larynx cancer, kidney cancer (e.g., renal cell carcinoma and Wilms tumor), gastric cancer, blastoma (e.g., nephroblastoma, medulloblastoma, hemangioblastoma, neuroblastoma, and retinoblastoma), polycythemia vera, chordoma, synovioma, mesothelioma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, cystadenocarcinoma, bile duct carcinoma, choriocarcinoma, epithelial carcinoma, ependymoma, pinealoma, acoustic neuroma, schwannoma, meningioma, pituitary adenoma, nerve sheath tumor, cancer of the small intestine, cancer of the endocrine system, cancer of the penis, cancer of the urethra, cutaneous or intraocular melanoma, a gynecologic tumor, solid tumors of childhood, and neoplasms of the central nervous system. Radiation therapy includes the administration of a radioactive agent to a patient or exposure of a patient to radiation. The radiation may be generated from sources such as

particle accelerators and related medical devices or agents that emit, e.g., X-radiation, gamma radiation, or electron (Beta radiation) beams. A treatment may be or further include surgery, e.g., to remove a tumor from a subject or living organism.

Other features and advantages of the invention will be apparent from the following Detailed Description, the drawings, and the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a graph grouping predicted sensitivity to irifolven by cancer type. Each gray circle represents the predicted irifolven sensitivity of one patient calculated as the difference between the mean of the expression levels of the biomarkers of sensitivity and the mean of the expression levels of the biomarkers of resistance for the patient. Patients are grouped according to cancer type. The median predicted sensitivity (black bar) for a cancer type is related to the relative response rate for that cancer type. The predictions are used for relative comparisons to compare cancer types and cannot be used for absolute predictions of response rate for a given cancer type. The predictions are normalized to a scale of 0 to 100 for all 3,522 patients.

DETAILED DESCRIPTION OF THE INVENTION

I have discovered that the expression levels of the biomarkers shown in Tables 1-4 may be detected in a patient having cancer and are useful for predicting the responsiveness of the patient to irifolven. These patients may already be determined to be resistance to a therapy other than irifolven, such as docetaxel, cabazitaxel, mitoxantrone, estramustine, prednisone, carboplatin, bevacizumab, paclitaxel, gemcitabine, doxorubicin, topotecan, etoposide, tamoxifen, letrozole, sorafenib, fluorouracil, capecitabine, oxaliplatin, interferon-alpha, 5-fluorouracil (5-FU), a histone deacetylase (HDAC) inhibitor, ipilimumab, bortezomib, carfilzomib, thalidomide, lenalidomide, pomalidomide, dexamethasone, cyclophosphamide, vincristine, melphalan, tegafur, irinotecan, cetuximab, leucovorin, SN-38, everolimus, temsirolimus, bleomycin, lomustine, depsipeptide, erlotinib, cisplatin, busulfan, epirubicin, arsenic trioxide, bendamustine, fulvestrant, teniposide, adriamycin, decitabine, estramustine, azaguanine, aclarubicin, mitomycin, paclitaxel, taxotere, APO010, ara-c, methylprednisolone, methotrexate, methyl-gag, belinostat, idarubicin, IL4-PR38, valproic acid, all-trans retinoic acid (ATRA), cytoxan, suberoylanilide hydroxamic acid, leukeran, fludarabine, vinblastine, dacarbazine, hydroxyurea, tegafur, daunorubicin, mechlorethamine, streptozocin, carmustine, mercaptopurine, dactinomycin, tretinoin, ifosfamide, floxuridine, thioguanine, PSC 833, herceptin, celecoxib, iressa, anastrozole, or rituximab.

A device, such as a microarray, with one or more single-stranded oligonucleotide probes that have substantial identity (e.g., at least 85%, 90%, 95%, 99%, or 100% sequence identity) to a sequence that is complementary or identical to the nucleic acid sequence of one or more biomarkers shown in Tables 1-4 can be used according to the methods described herein to assess the responsiveness of a cancer patient to treatment with irifolven. For example, the probes can be used to detect one or more (e.g., two, three, four, five, ten, twenty, or all) of the biomarkers of sensitivity listed in Tables 1 and 3, such as ATP1B1 (SEQ ID NO: 201 or 219), in a sample (e.g., a tumor sample) from a patient having

cancer (e.g., prostate cancer, ovarian cancer, or hepatocellular carcinoma (HCC)). Additionally, the probes can be used to detect one or more (e.g., two, three, four, five, ten, twenty, or all) of the biomarkers of resistance listed in Tables 2 and 4, such as IGLC1 (SEQ ID NO: 301, 302, 303, or 318), in a sample (e.g., a tumor sample) from a patient having cancer (e.g., prostate cancer, ovarian cancer, or hepatocellular carcinoma (HCC)).

Accordingly, the invention features individual biomarkers (e.g., ATP1B1 (SEQ ID NO: 201 or 219) or IGLC1 (SEQ ID NO: 301, 302, 303, or 318)) and sets of biomarkers shown in Tables 1-4 that can be used to determine the responsiveness of a cancer patient to irifolven at various stages of disease progression (e.g., patients diagnosed with cancer or patients after cancer recurrence) and at different times during the treatment process (e.g., prior to administration of any cancer treatment, after administration of one or more cancer treatments other than irifolven, prior to administration of irifolven, or during administration of irifolven). Additionally, the methods can be used to determine the irifolven responsiveness of a patient with cancer that is resistant to one or more cancer therapies other than irifolven, such as docetaxel, cabazitaxel, mitoxantrone, estramustine, prednisone, carboplatin, bevacizumab, paclitaxel, gemcitabine, doxorubicin, topotecan, etoposide, tamoxifen, letrozole, sorafenib, fluorouracil, capecitabine, oxaliplatin, interferon-alpha, 5-fluorouracil (5-FU), a histone deacetylase (HDAC) inhibitor, ipilimumab, bortezomib, carfilzomib, thalidomide, lenalidomide, pomalidomide, dexamethasone, cyclophosphamide, vincristine, melphalan, tegafur, irinotecan, cetuximab, leucovorin, SN-38, everolimus, temsirolimus, bleomycin, lomustine, depsipeptide, erlotinib, cisplatin, busulfan, epirubicin, arsenic trioxide, bendamustine, fulvestrant, teniposide, adriamycin, decitabine, estramustine, azaguanine, aclarubicin, mitomycin, paclitaxel, taxotere, APO010, ara-c, methylprednisolone, methotrexate, methyl-gag, belinostat, idarubicin, IL4-PR38, valproic acid, all-trans retinoic acid (ATRA), cytoxan, suberoylanilide hydroxamic acid, leukeran, fludarabine, vinblastine, dacarbazine, hydroxyurea, tegafur, daunorubicin, mechlorethamine, streptozocin, carmustine, mercaptopurine, dactinomycin, tretinoin, ifosfamide, floxuridine, thioguanine, PSC 833, herceptin, celecoxib, iressa, anastrozole, or rituximab.

In particular, the invention provides methods for determining whether a patient may be responsive to irifolven by, e.g., detecting the expression level (e.g., mRNA or protein produced therefrom) of one or more of the biomarkers shown in Tables 1-4 (e.g., ATP1B1 (SEQ ID NO: 201 or 219)) in a biological sample (e.g., a tumor biopsy) obtained from the subject using a device (e.g., a microarray or a protein array). The expression level of one or more of the biomarkers of sensitivity may then be compared to the expression level of the biomarkers in a cell or tissue known to be sensitive or resistant to irifolven to determine the patient's responsiveness to irifolven. The patient may be responsive to irifolven if the expression level of the one or more of the biomarkers of sensitivity (e.g., one or more of ATP1B1 (SEQ ID NO: 201 or 219), UCHL1 (SEQ ID NO: 202), PTGR1 (SEQ ID NO: 203 or 210), NME7 (SEQ ID NO: 204), PLS3 (SEQ ID NO: 205), S100A10 (SEQ ID NO: 206), CD24 (SEQ ID NO: 207, 209, or 220), NQO1 (SEQ ID NO: 208 or 216), MYOF (SEQ ID NO: 211), LAPTM4B (SEQ ID NO: 212), CALD1 (SEQ ID NO: 213), PDGFC (SEQ ID NO: 214), BASP1 (SEQ ID NO: 215), ID1 (SEQ ID NO: 217), and GJA1 (SEQ ID NO: 218)) is substantially similar to the expression level of the biomarkers of sensitivity in a cell or tissue known to be sensitive to irifolven

(e.g., from a patient sensitive to irifolven). The patient may also be responsive to irifolven if the level of expression of one or more of the biomarkers of resistance (e.g., one or more of IGLC1 (SEQ ID NO: 301, 302, 303, or 318), LAPTM5 (SEQ ID NO: 304 or 338), ARHGDIB (SEQ ID NO: 305 or 311), SLC43A3 (SEQ ID NO: 307), LCP1 (SEQ ID NO: 308), HCLS1 (SEQ ID NO: 309), CD53 (SEQ ID NO: 310), MZB1 (SEQ ID NO: 313), RASSF5 (SEQ ID NO: 314 or 386), FAM46C (SEQ ID NO: 315), RCSD1 (SEQ ID NO: 316), IGJ (SEQ ID NO: 317), LPXN (SEQ ID NO: 319), ITGB7 (SEQ ID NO: 320), and GTSF1 (SEQ ID NO: 321)) is substantially dissimilar to the expression level of the biomarkers of resistance in a cell or tissue known to be resistant to irifolven (e.g., from a patient resistant to irifolven).

The invention also features methods of treating a patient having cancer, such as a patient having a cancer that is resistant to one or more cancer therapies other than irifolven, by detecting the expression levels of one or more of the biomarkers shown in Tables 1-4 (e.g., ATP1B1 (SEQ ID NO: 201)) in a sample (e.g., a tumor sample) from the patient, and then administering irifolven based on the expression levels of the biomarkers. In particular, a patient having cancer may be administered irifolven if the expression level of one or more biomarkers of sensitivity is substantially similar to the expression level of the biomarkers of sensitivity in a cell or tissue known to be sensitive to irifolven. Additionally, a patient having cancer may be administered irifolven if the expression level of one or more biomarkers of resistance is substantially dissimilar to the expression level of the biomarkers of resistance in a cell or tissue known to be resistant to irifolven. Thus, the methods can be used to treat cancer patients predicted to be responsive to irifolven, such as patients having, e.g., prostate cancer, ovarian cancer, hepatocellular carcinoma (HCC), cervical cancer, renal cell carcinoma (RCC), esophageal cancer, melanoma, glioma, pancreatic cancer, gastrointestinal stromal tumors (GIST), sarcoma, estrogen receptor-positive (ERpos) breast cancer, non-small cell lung carcinoma (NSCLC), colon cancer, bladder cancer, squamous cell carcinoma of the head and neck (SCCHN), acute myelogenous leukemia (AML), acute lympho-blastic leukemia (ALL), chronic lymphocytic leukemia (CLL), myelodysplastic syndrome (MDS), chronic myelogenous leukemia-chronic phase (CMLCP), diffuse large B-cell lymphoma (DLBCL), cutaneous T-cell lymphoma (CTCL), peripheral T-cell lymphoma (PTCL), and Hodgkin's lymphoma. Alternatively, a patient having cancer may not be administered irifolven if the expression level of one or more biomarkers of sensitivity is substantially dissimilar to the expression level of the biomarkers of sensitivity in a cell or tissue known to be sensitive to irifolven. Likewise, a patient having cancer may not be administered irifolven if the expression level of one or more biomarkers of resistance is substantially similar to the expression level of the biomarkers of resistance in a cell or tissue known to be resistant to irifolven.

Methods are described herein for identifying biomarkers of drug responsiveness, detecting biomarker gene expression in cancer patients, determining the responsiveness of a cancer patient to irifolven, and treating cancer patients with irifolven. Also described are devices and kits for use in these methods.

Methods for Identifying Biomarkers of Drug Responsiveness

The invention features methods for identifying biomarkers (e.g., one or more of the biomarkers of Tables 1-4) for

determining the responsiveness of a cancer patient to a cancer treatment, such as irifolven. Such methods can involve, for example, an algorithm based on growth inhibition values (GI50) of cell lines (e.g., NCI60 cell lines) subjected to treatment with irifolven, followed by measurement of gene expression (e.g., using a microarray (e.g., an Affymetrix HG-U133A or HG-U133_Plus_2 array)).

Methodology of the In Vitro Cancer Growth Inhibition Screen

The human tumor cell lines of the cancer screening panel may be grown in RPMI 1640 medium containing 5% fetal bovine serum and 2 mM L-glutamine. Cells may be inoculated into 96 well microtiter plates in 100 μ L at plating densities ranging from 5,000 to 40,000 cells/well depending on the doubling time of individual cell lines. After cell inoculation, the microtiter plates may be incubated at 37° C., 5% CO₂, 95% air and 100% relative humidity for 24 hours prior to addition of experimental compounds.

After 24 hours, two plates of each cell line may be fixed in situ with TCA, to represent a measurement of the cell population for each cell line at the time of compound addition (Tz). Experimental compounds may be solubilized in dimethyl sulfoxide at 400-fold the desired final maximum test concentration and stored frozen prior to use. At the time of compound (e.g., irifolven) addition, an aliquot of frozen concentrate may be thawed and diluted to twice the desired final maximum test concentration with complete medium containing 50 μ g/ml Gentamicin. A total of four additional 10-fold or 1/2 log serial dilutions are made to provide a total of five concentrations plus control. Aliquots of 100 μ L of these different compound dilutions are added to the appropriate microtiter wells already containing 100 μ L of medium, resulting in the required final compound concentrations.

Following compound (e.g., irifolven) addition, the plates may be incubated for an additional 48 h at 37° C., 5% CO₂, 95% air, and 100% relative humidity. For adherent cells, the assay may be terminated by the addition of cold TCA. Cells may be fixed in situ by the gentle addition of 50 μ L of cold 50% (w/v) TCA (final concentration, 10% TCA) and incubated for 60 minutes at 4° C. The supernatant may be discarded, and the plates may be washed five times with tap water and air-dried. Sulforhodamine B (SRB) solution (100 μ L) at 0.4% (w/v) in 1% acetic acid may be added to each well, and the plates may be incubated for 10 minutes at room temperature. After staining, unbound dye may be removed by washing five times with 1% acetic acid and the plates may be air-dried. Bound stain may be subsequently solubilized with 10 mM trizma base, and the absorbance may be read on an automated plate reader at a wavelength of 515 nm. For suspension cells, the methodology may be the same, except that the assay may be terminated by fixing settled cells at the bottom of the wells by gently adding 50 μ L of 80% TCA (final concentration, 16% TCA). Using the seven absorbance measurements [time zero, (Tz), control growth, (C), and test growth in the presence of compound (e.g., irifolven) at the five concentration levels (Ti)], the percentage growth may be calculated at each of the compound concentrations levels. Percentage growth inhibition may be calculated as:

$$\frac{[(Ti - Tz)/(C - Tz)] \times 100}{\text{for concentrations for which } Ti \geq Tz}$$

$$\frac{[(Ti - Tz)/Tz] \times 100}{\text{for concentrations for which } Ti < Tz}$$

Three dose response parameters may be calculated for each experimental agent (e.g., irifolven). Growth inhibition of 50% (GI50) is calculated from $[(Ti - Tz)/(C - Tz)] \times$

100=50, which is the agent (e.g., irifolven) concentration resulting in a 50% reduction in the net protein increase (as measured by SRB staining) in control cells during the compound incubation. The compound concentration resulting in total growth inhibition (TGI) is calculated from $T_i=T_z$. The LC50 (concentration of compound resulting in a 50% reduction in the measured protein at the end of the compound treatment as compared to that at the beginning) indicating a net loss of cells following treatment is calculated from $[(T_i-T_z)/T_z] \times 100 = -50$. Values are calculated for each of these three parameters if the level of activity is reached; however, if the effect is not reached or is exceeded, the value for that parameter is expressed as greater or less than the maximum or minimum concentration tested.

Gene Expression and Growth Inhibition Analysis

The gene expression measurements of NCI60 cancer cell lines can be obtained from a publically available database (e.g., the National Cancer Institute and the Massachusetts Institute of Technology). Each dataset can be normalized so that sample expression measured by different chips can be compared. The preferred method of normalization is the logit transformation, which may be performed for each gene y on each chip, as follows:

$$\text{logit}(y) = \log [(y - \text{background}) / (\text{saturation} - y)],$$

where background is calculated as the minimum intensity measured on the chip minus 0.1% of the signal intensity range: $\text{min} - 0.001 * (\text{max} - \text{min})$, and saturation is calculated as the maximum intensity measured on the chip plus 0.1% of the signal intensity range: $\text{max} + 0.001 * (\text{max} - \text{min})$. The resulting logit transformed data may then be z-transformed to mean zero and standard deviation 1.

Next, gene expression can be correlated to cancer cell growth inhibition. Growth inhibition data (GI50) of the NCI60 cell lines in the presence of a cancer treatment, such as irifolven, can be obtained from the NCI. The correlation between the logit-transformed expression level of each gene in each cell line and the logarithm of GI50 (the concentration of a given compound that results in a 50% inhibition of growth) can be calculated, e.g., using the Pearson correlation coefficient or the Spearman Rank-Order correlation coefficient. Instead of using GI50s, any other measure of patient sensitivity to a given treatment (e.g., irifolven) may be correlated to gene expression levels of the patient. Since a plurality of measurements may be available for a single gene, the most accurate determination of correlation coefficient can be, e.g., the median of the correlation coefficients calculated for all probes measuring expression of the same gene.

For example, the median correlation coefficient of gene expression measured on a probe to growth inhibition or patient sensitivity to irifolven can be calculated for all genes of interest. Genes that have a median correlation above, e.g., 0.20, 0.21, 0.22, 0.23, 0.24, 0.25, 0.26, 0.27, 0.28, 0.29, 0.30, 0.31, 0.32, 0.33, 0.34, 0.35, 0.36, 0.37, 0.38, 0.39, 0.40, or higher (e.g., 0.2 or higher), can be used as biomarkers of sensitivity for assessing responsiveness of a cancer patient (e.g., a patient having cancer that is resistant to one or more cancer therapies other than irifolven) to irifolven. Likewise, genes that have a median correlation below, e.g., -0.20, -0.21, -0.22, -0.23, -0.24, -0.25, -0.26, -0.27, -0.28, -0.29, -0.30, -0.31, -0.32, -0.33, -0.34, -0.35, -0.36, -0.37, -0.38, -0.39, -0.40, or lower (e.g., -0.2 or lower), can be used as biomarkers of resistance for assessing responsiveness of a cancer patient (e.g., a patient having cancer that is resistant to one or more cancer therapies other than irifolven) to irifolven. Preferably, the correlation coefficient

of a biomarker of sensitivity will exceed 0.2, while the correlation coefficient of a biomarker of resistance will be less than -0.2. The result is a list of biomarker genes that correlate to sensitivity or resistance to irifolven, as shown in Tables 1 and 3 and Tables 2 and 4, respectively.

Cancer Types

The methods, devices, and kits of the invention can be used for diagnosing, prognosing, monitoring, treating, and/or reducing cancer in a subject suffering from, diagnosed with, or susceptible to cancer. Non-limiting examples of cancers that can be diagnosed, prognosed, monitored, treated, or reduced using the methods include hematological and solid tumors. In particular, cancers include, e.g., prostate cancer, ovarian cancer (e.g., ovarian adenocarcinoma or embryonal carcinoma), liver cancer (e.g., hepatocellular carcinoma (HCC) or hepatoma), myeloma (e.g., multiple myeloma), colorectal cancer (e.g., colon cancer and rectal cancer), leukemia (e.g., acute myeloid leukemia, acute lymphoid leukemia, chronic myeloid leukemia, chronic lymphocytic leukemia, acute myeloblastic leukemia, acute promyelocytic leukemia, acute myelomonocytic leukemia, acute monocytic leukemia, acute erythroleukemia, and chronic leukemia), myelodysplastic syndrome, lymphoma (e.g., diffuse large B-cell lymphoma, cutaneous T-cell lymphoma, peripheral T-cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, Waldenstrom's macroglobulinemia, and lymphocytic lymphoma), cervical cancer, esophageal cancer, melanoma, glioma (e.g., oligodendroglioma), pancreatic cancer (e.g., adenosquamous carcinoma, signet ring cell carcinoma, hepatoid carcinoma, colloid carcinoma, islet cell carcinoma, and pancreatic neuroendocrine carcinoma), gastrointestinal stromal tumor, sarcoma (e.g., fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, leiomyosarcoma, Ewing's sarcoma, and rhabdomyosarcoma), breast cancer (e.g., medullary carcinoma), ER-positive cancer, bladder cancer, head and neck cancer (e.g., squamous cell carcinoma of the head and neck), lung cancer (e.g., non-small cell lung carcinoma, large cell carcinoma, bronchogenic carcinoma, and papillary adenocarcinoma), metastatic cancer, oral cavity cancer, uterine cancer, testicular cancer (e.g., seminoma and embryonal carcinoma), skin cancer (e.g., squamous cell carcinoma and basal cell carcinoma), thyroid cancer (e.g., papillary carcinoma and medullary carcinoma), brain cancer (e.g., astrocytoma and craniopharyngioma), stomach cancer, intra-epithelial cancer, bone cancer, biliary tract cancer, eye cancer, larynx cancer, kidney cancer (e.g., renal cell carcinoma and Wilms tumor), gastric cancer, blastoma (e.g., nephroblastoma, medulloblastoma, hemangioblastoma, neuroblastoma, and retinoblastoma), polycythemia vera, chordoma, synovioma, mesothelioma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, cystadenocarcinoma, bile duct carcinoma, choriocarcinoma, epithelial carcinoma, ependymoma, pinealoma, acoustic neuroma, schwannoma, meningioma, pituitary adenoma, nerve sheath tumor, cancer of the small intestine, cancer of the endocrine system, cancer of the penis, cancer of the urethra, cutaneous or intraocular melanoma, a gynecologic tumor, solid tumors of childhood, and neoplasms of the central nervous system.

In particular, the methods are useful for diagnosing, prognosing, monitoring, treating, or preventing, e.g., prostate cancer, ovarian cancer, hepatocellular carcinoma (HCC), cervical cancer, renal cell carcinoma (RCC), esophageal cancer, melanoma, glioma, pancreatic cancer, gastrointestinal stromal tumors (GIST), sarcoma, estrogen recep-

tor-positive (ERpos) breast cancer, non-small cell lung carcinoma (NSCLC), colon cancer, bladder cancer, squamous cell carcinoma of the head and neck (SCCHN), acute myelogenous leukemia (AML), acute lympho-blastic leukemia (ALL), chronic lymphocytic leukemia (CLL), myelodysplastic syndrome (MDS), chronic myelogenous leukemia-chronic phase (CMLCP), diffuse large B-cell lymphoma (DLBCL), cutaneous T-cell lymphoma (CTCL), peripheral T-cell lymphoma (PTCL), and Hodgkin's lymphoma.

For example, the cancer can be prostate cancer, such as Stage I, II (e.g., IIA or IIB), III, or IV prostate cancer. In particular, the cancer may be prostate cancer that is resistant to one or more cancer therapies, such as docetaxel, cabazitaxel, mitoxantrone, estramustine, prednisone, and/or surgery. Alternatively, the cancer is an ovarian cancer. The ovarian cancer can be, for example, a Stage I (e.g., Stage IA, IB, or IC), Stage II (e.g., Stage IIA or IIB), Stage III (e.g., Stage IIIA1, IIIA2, IIIB, or IIIC), or Stage IV (e.g., Stage IVA or IVB) ovarian cancer. In particular, the cancer can be ovarian cancer that is resistant to one or more cancer therapies, such as docetaxel, carboplatin, bevacizumab, paclitaxel, gemcitabine, doxorubicin, topotecan, etoposide, tamoxifen, and/or letrozole. Additionally, the cancer can be HCC, such as Stage I, Stage II, Stage III (e.g., Stage IIIA, IIIB, or IIIC), or Stage IV (e.g., Stage IVA or IVB) HCC. In particular, the cancer can be HCC that is resistant to one or more cancer therapies, such as sorafenib, doxorubicin, cisplatin, gemcitabine, capecitabine, oxaliplatin, interferon-alpha, and/or 5-fluorouracil (5-FU).

Methods for Detecting Biomarker Gene Expression in Cancer Patients

A cancer patient can be assessed for sensitivity or resistance to irifolven by detecting gene expression of a biomarker (e.g., one or more of the biomarkers of Tables 1-4) in a biological sample obtained from the cancer patient (e.g., a patient having cancer that is resistant to one or more cancer therapies other than irifolven). The biological sample can include, for example, cells, tissue (e.g., a tissue sample obtained by biopsy), blood, serum, plasma, urine, sputum, cerebrospinal fluid, lymph tissue or fluid, or pancreatic fluid. For example, the biological sample can be fresh frozen or formalin-fixed paraffin embedded (FFPE) tissue obtained from the subject, such as a tumor sample (e.g., a biopsy) from the tissue of interest (e.g., prostate, ovarian, lung, lymph nodes, thymus, spleen, bone marrow, breast, colorectal, pancreatic, cervical, bladder, gastrointestinal, head, or neck tissue).

RNA Extraction and Biomarker Expression Measurement

Cell samples or tissue samples may be snap frozen in liquid nitrogen until processing. RNA may be extracted using, e.g., Trizol Reagent from Invitrogen following manufacturer's instructions, and detected directly or converted to cDNA for detection. RNA may be amplified using, e.g., MessageAmp kit from Ambion following manufacturer's instructions. Amplified RNA may be quantified using, e.g., HG-U133A or HG-U133_Plus2 GeneChip from Affymetrix Inc. or a compatible apparatus, e.g., the GCS3000Dx GeneChip® System from Affymetrix Inc., using the manufacturer's instructions. The resulting biomarker expression measurements may be further analyzed as described herein. The procedures described can be implemented using, e.g., R software available from R-Project and supplemented with packages available from Bioconductor.

One or more of the biomarkers shown in Tables 1-4 (e.g., ATP1B1 (SEQ ID NO: 201)) may be measured in a biological sample (e.g., a tumor sample) obtained from the

cancer patient (e.g., a patient with any of the cancer types described herein, such as a patient having cancer that is resistant to one or more cancer therapies other than irifolven) using, e.g., polymerase chain reaction (PCR), reverse transcriptase PCR (RT-PCR), quantitative real-time PCR (qRT-PCR), an array (e.g., a microarray), a genechip, pyrosequencing, nanopore sequencing, sequencing by synthesis, sequencing by expansion, single molecule real time technology, sequencing by ligation, microfluidics, infrared fluorescence, next generation sequencing (e.g., RNA-Seq techniques), Northern blots, Western blots, Southern blots, NanoString nCounter technologies (e.g., those described in U.S. Patent Application Nos. US 2011/0201515, US 2011/0229888, and US 2013/0017971, each of which is incorporated by reference in its entirety), proteomic techniques (e.g., mass spectrometry or protein arrays), and combinations thereof.

Devices

Devices of the invention can be used for detecting the level of expression of one or more biomarkers shown in Tables 1-4. The device may include at least one single-stranded nucleic acid (e.g., a probe) having at least 85% sequence identity (e.g., 85%, 90%, 95%, 97%, 98%, 99%, or 100% sequence identity) to a nucleic acid sequence that is complementary or identical to at least 5 (e.g., at least 10, at least 15, at least 20, or more) consecutive nucleotides of one or more biomarkers shown in Tables 1-4 (e.g., ATP1B1 (SEQ ID NO: 201 or 219) or IGLC1 (SEQ ID NO: 301, 302, 303, or 318)), in which the at least one single-stranded nucleic acid is sufficient for the detection of the expression level of the one or more biomarkers. The device may be used to detect the expression level of a given biomarker by specific hybridization between the single-stranded nucleic acid and the biomarker (e.g., an mRNA, genomic DNA, or non-coding RNA), a nucleic acid encoding the biomarker (e.g., an mRNA), or a complementary nucleic acid thereof. The device may be or include a microarray. The device may also include or be used with reagents and materials for next generation sequence (e.g., sequencing by synthesis). The device may also include or be used with NanoString reagents and at least one nCounter cartridge. The device may be or include a protein array, which contains one or more protein binding moieties (e.g., proteins, antibodies, nucleic acids, aptamers, affibodies, lipids, phospholipids, small molecules, labeled variants of any of the above, and any other moieties useful for protein detection as well known in the art) capable of detectably binding to the polypeptide product(s) of one or more biomarkers shown in Tables 1-4. The device may also be a cartridge for measuring an amplification product resulting from hybridization between one or more nucleic acid molecules from the patient and at least one single-stranded nucleic acid single-stranded nucleic acid molecules of the device, such as a device for performing qRT-PCR.

Microarrays

The expression levels of the biomarkers (e.g., the biomarkers listed in Tables 1-4 (e.g., ATP1B1 (SEQ ID NO: 201))) may be determined using high-throughput expression profiling platforms, such as microarrays. In particular, a microarray for use in the methods for assessing the responsiveness of a cancer patient (e.g., a patient having cancer that is resistant to one or more cancer therapies other than irifolven) to irifolven contains or is produced by generating oligonucleotide probes (e.g., DNA, cDNA, or RNA probes) capable of hybridizing to one or more biomarkers of interest (e.g., one or more of the biomarkers of Tables 1-4) or the complement sequences thereof. Each probe can have, e.g., at

least 10, 15, 20, 25, 30, or more contiguous nucleic acid residues (e.g., at least 15) that are complementary or identical to a nucleic acid sequence of a selected biomarker. The probe nucleic sequence can also have at least 85% (e.g., 90%, 95%, 99%, or 100%) sequence identity to the nucleic acid sequence of the gene coding the biomarker (e.g., ATP1B1 (SEQ ID NO: 201 or 219)) or the complement sequence thereof. In particular, the probe sequences can be complementary to all or a portion of the nucleic acid sequence of the biomarker(s).

For example, microarrays of the invention for determining irofulven responsiveness can include probes for one or more (e.g., at least 5, 10, 15, or 20 or more (e.g., all)) biomarkers of sensitivity shown in Tables 1 and 3, such as ATP1B1 (SEQ ID NO: 201 or 219), UCHL1 (SEQ ID NO: 202), PTGR1 (SEQ ID NO: 203 or 210), NME7 (SEQ ID NO: 204), PLS3 (SEQ ID NO: 205), S100A10 (SEQ ID NO: 206), CD24 (SEQ ID NO: 207, 209, or 220), NQO1 (SEQ ID NO: 208 or 216), MYOF (SEQ ID NO: 211), LAPTM4B (SEQ ID NO: 212), CALD1 (SEQ ID NO: 213), PDGFC (SEQ ID NO: 214), BASP1 (SEQ ID NO: 215), ID1 (SEQ ID NO: 217), and/or GJA1 (SEQ ID NO: 218). Microarrays for determining irofulven responsiveness can also include probes for one or more (e.g., at least 5, 10, 15, or 20 or more (e.g., all)) biomarkers of resistance listed in Tables 2 and 4, such as IGLC1 (SEQ ID NO: 301, 302, 303, or 318), LAPTM5 (SEQ ID NO: 304 or 338), ARHGDIB (SEQ ID NO: 305 or 311), SLC43A3 (SEQ ID NO: 307), LCP1 (SEQ ID NO: 308), HCLS1 (SEQ ID NO: 309), CD53 (SEQ ID NO: 310), MZB1 (SEQ ID NO: 313), RASSF5 (SEQ ID NO: 314 or 386), FAM46C (SEQ ID NO: 315), RCSD1 (SEQ ID NO: 316), IGJ (SEQ ID NO: 317), LPXN (SEQ ID NO: 319), ITGB7 (SEQ ID NO: 320), and/or GTSF1 (SEQ ID NO: 321). Microarrays for determining irofulven responsiveness can also include probes for one or more (e.g., at least 5, 10, 15, or 20 or more (e.g., all)) biomarkers of sensitivity and biomarkers of resistance shown in Tables 1-4, such as ATP1B1 (SEQ ID NO: 201 or 219), UCHL1 (SEQ ID NO: 202), PTGR1 (SEQ ID NO: 203 or 210), NME7 (SEQ ID NO: 204), PLS3 (SEQ ID NO: 205), S100A10 (SEQ ID NO: 206), CD24 (SEQ ID NO: 207, 209, or 220), NQO1 (SEQ ID NO: 208 or 216), MYOF (SEQ ID NO: 211), LAPTM4B (SEQ ID NO: 212), CALD1 (SEQ ID NO: 213), PDGFC (SEQ ID NO: 214), BASP1 (SEQ ID NO: 215), ID1 (SEQ ID NO: 217), GJA1 (SEQ ID NO: 218), IGLC1 (SEQ ID NO: 301, 302, 303, or 318), LAPTM5 (SEQ ID NO: 304 or 338), ARHGDIB (SEQ ID NO: 305 or 311), SLC43A3 (SEQ ID NO: 307), LCP1 (SEQ ID NO: 308), HCLS1 (SEQ ID NO: 309), CD53 (SEQ ID NO: 310), MZB1 (SEQ ID NO: 313), RASSF5 (SEQ ID NO: 314 or 386), FAM46C (SEQ ID NO: 315), RCSD1 (SEQ ID NO: 316), IGJ (SEQ ID NO: 317), LPXN (SEQ ID NO: 319), ITGB7 (SEQ ID NO: 320), and/or GTSF1 (SEQ ID NO: 321).

A microarray probe may be single-stranded or double-stranded. The probe may be labeled (e.g., detectably labeled with a fluorescent molecule, dye molecule, small molecule, epitope tag, barcode sequence, polypeptide, or any other detectable molecule). Probes can be detectably labeled and immobilized on a solid support to form the microarray. For example, probes can be either prefabricated and spotted to the surface or directly synthesized on to the surface (in situ) of the microarray. The microarray can also be configured such that the sequence and position of each member (e.g., probe) of the array is known. For example, a selection of biomarkers whose expression correlates with an increased likelihood of responsiveness to irofulven can be arrayed on

a solid support. Hybridization of a labeled probe with a particular target nucleic acid (e.g., an mRNA corresponding to one or more biomarkers of Tables 1-4) indicates that the sample from which the mRNA was derived expresses that biomarker (e.g., the biomarker of sensitivity or resistance to irofulven).

PCR-Based Techniques

As few as one to thirty (e.g., 5 to 30 or 10 to 30, or at least the first 15 of the biomarkers listed in Tables 1-2) biomarkers may be used to determine patient responsiveness to irofulven using the methods described herein. Tissue or cell samples from a cancer patient (e.g., a patient having cancer that is resistant to one or more cancer therapies other than irofulven) can be conveniently assayed for gene expression levels using polymerase chain reaction (PCR) analysis, such as quantitative real-time PCR (qPCR), or quantitative loop-mediated isothermal amplification (q-LAMP). For example, an mRNA corresponding to a biomarker of Tables 1-4 can be detected in a biological sample by (a) producing cDNA from the sample by reverse transcription using at least one primer; (b) amplifying the cDNA so produced using a target polynucleotide as sense and antisense primers to amplify target cDNAs therein; and (c) detecting the presence of the amplified target cDNA using polynucleotide probes. The primers and probes including the target sequences shown in Tables 1-4, such as ATP1B1 (SEQ ID NO: 201 or 219) and/or IGLC1 (SEQ ID NO: 301, 302, 303, or 318), may be used to detect expression of one or more of the indicated biomarkers using PCR. The methods can include one or more steps that allow determination of the levels of target mRNA in a biological sample (e.g., by simultaneously examining the levels of a comparative control mRNA sequence or "housekeeping" gene, such as an actin family member or GAPDH). The primers for these PCR-based assays may be labeled for detection according to methods known in the art.

Sequencing

The expression levels of the biomarkers shown in Tables 1-4, such as ATP1B1 (SEQ ID NO: 201 or 219) and/or IGLC1 (SEQ ID NO: 301, 302, 303, or 318), may be determined using sequencing technologies, such as next generation sequencing platforms (e.g., RNA-Seq), as described in Mortazavi et al., *Nat. Methods* 5: 621-628, 2008, hereby incorporated by reference. RNA-Seq is a robust technology for monitoring expression by direct sequencing of the RNA molecules in a sample. This methodology may include fragmentation of RNA to an average length of, e.g., 200 nucleotides, conversion to cDNA by random priming, and synthesis of double-stranded cDNA (e.g., using the PROTOSCRIPT® First Strand cDNA Synthesis Kit from New England Biosciences). The cDNA may then be converted into a molecular library for sequencing by addition of sequence adapters for each library (e.g., from ILLUMINA®/Solexa), and the resulting 50 to 100 nucleotide reads are mapped onto the genome. Exemplary sequencing platforms suitable for use according to the methods include, e.g., pyrosequencing, ILLUMINA® sequencing by synthesis, SOLID® sequencing, ION TORRENT® sequencing, and SMRT® sequencing.

Methods of Determining the Responsiveness of a Patient to Irofulven

The invention features diagnostic methods for the detection and screening of cancer patients (e.g., a patient having cancer that is resistant to one or more cancer therapies other than irofulven) that may be responsive to irofulven using one or more of the biomarkers shown in Tables 1-4 (e.g., ATP1B1 (SEQ ID NO: 201 or 219) or IGLC1 (SEQ ID NO: 301, 302, 303, or 318)). The methods of the invention may

be used for predicting a patient's responsiveness to irifolven, and optionally, treating the cancer patient throughout the progression of cancer and/or in cases of recurrence (e.g., after a first line treatment, a second line treatment, and/or a third line treatment).

The invention provides individual biomarkers (e.g., ATP1B1 (SEQ ID NO: 201)) and sets of biomarkers (e.g., two or more of the biomarkers listed in Tables 1-4), the expression levels of which, as detected in a biological sample (e.g., a tumor sample, such as a biopsy) obtained from a cancer patient (e.g., a human with cancer), are indicative of responsiveness to irifolven. The biomarkers were identified using methods similar to those previously described in, e.g., Chen et al. (*Mol. Cancer Ther.* 11:34-33, 2012), Wang et al. (*J. Nat. Cancer Inst.* 105: 1284-1291, 2013), and Knudsen et al. (*PLoS One*, 9: e87415, 2014), each of which are incorporated by reference herein in their entirety. In particular, an algorithm based on growth inhibition values (GI50) of a cell line (e.g., NCI60 cells) is subjected to treatment with irifolven and gene expression is determined (e.g., by microarray analysis, reverse transcriptase polymerase chain reaction (RT-PCR), quantitative real-time PCR (qPCR), or next generation sequencing). After normalization, genes with, e.g., a Pearson correlation coefficient greater than about 0.2 or below about -0.2 can be classified as biomarkers of sensitivity or resistance, respectively. In particular, a correlation coefficient of about 0.2 or greater is a statistically significant cut-off known in the art for establishing whether the expression level of A GENE, e.g., the genes shown in Tables 1-4, correlate with the likelihood of cancer treatment sensitivity, such as sensitivity to irifolven. Thus, a correlation coefficient of about 0.2 or greater or about -0.2 or lower can be used to estimate the statistical significance of the expression level of the genes of Tables 1-4 for predicting patient responsiveness to treatment with irifolven according to the methods described herein.

Comparison of Biomarker Expression Levels

One or more biomarkers of sensitivity and/or resistance, identified as described herein, can be used to predict responsiveness to irifolven by measuring the expression level of the biomarkers in a biological sample obtained from the cancer patient. A single biomarker (e.g., any of the biomarkers of Tables 1-4, such as ATP1B1 (SEQ ID NO: 201)) may be used to determine the responsiveness of a cancer patient (e.g., a patient having cancer that is resistant to one or more cancer therapies other than irifolven) to irifolven. After determining the expression level of the biomarker(s) in a sample (e.g., a tumor sample) from the cancer patient, the expression level of the biomarker(s) in the sample may be compared to the expression level of the biomarker(s) in a cell (e.g., a cancer cell) or tissue (e.g., a tumor tissue) known to be sensitive to treatment with irifolven. If the expression level of the biomarker(s) in the sample from the cancer patient is substantially similar (e.g., identical to or has the same trend of expression level) to the expression level of the biomarker(s) in the cell or tissue known to be sensitive to irifolven, then the cancer patient is predicted to be responsive to treatment with irifolven. Alternatively, if the expression level of the biomarker(s) in the sample from the cancer patient is substantially dissimilar to the expression level of the biomarker(s) in the cell or tissue known to be sensitive to irifolven, then the cancer patient is predicted to be non-responsive to treatment with irifolven.

The expression level of the biomarker (e.g., ATP1B1 (SEQ ID NO: 201)) in a sample from the cancer patient may also be compared to the expression level of the biomarker in a cell (e.g., a cancer cell) or tissue (e.g., a tumor tissue)

known to be resistant to treatment with irifolven. If the expression level of the biomarker in the sample from the cancer patient is substantially similar to the expression level of the biomarker in the cell or tissue known to be resistant to irifolven, then the cancer patient is predicted to be non-responsive to treatment with irifolven. Alternatively, if the expression level of the biomarker in the sample from the cancer patient is substantially dissimilar to the expression level of the biomarker in the cell or tissue known to be sensitive to irifolven, then the cancer patient is predicted to be responsive to treatment with irifolven.

The responsiveness of a cancer patient (e.g., a patient having cancer that is resistant to one or more cancer therapies other than irifolven) to irifolven can also be predicted by comparing the expression level of a biomarker (e.g., ATP1B1 (SEQ ID NO: 201)) to the expression level of the biomarker in one or more cells or tissues (e.g., from a cancer patient population) known to be sensitive to treatment with irifolven and one or more cells or tissues (e.g., from a cancer patient population) known to be resistant to treatment with irifolven. In particular, the patient may be responsive to treatment with irifolven if the expression level of the biomarker is more similar to the expression level of the biomarker in a cell or tissue known to be sensitive to treatment with irifolven than to a cell or tissue known to be resistant to treatment with irifolven. Alternatively, the patient may be non-responsive to treatment with irifolven if the expression level of the biomarker is more similar to the expression level of the biomarker in a cell or tissue known to be resistant to treatment with irifolven than to a cell or tissue known to be sensitive to treatment with irifolven.

Additionally, one or more biomarkers of sensitivity (e.g., one or more of ATP1B1 (SEQ ID NO: 201 or 219), UCHL1 (SEQ ID NO: 202), PTGR1 (SEQ ID NO: 203 or 210), NME7 (SEQ ID NO: 204), PLS3 (SEQ ID NO: 205), S100A10 (SEQ ID NO: 206), CD24 (SEQ ID NO: 207, 209, or 220), NQO1 (SEQ ID NO: 208 or 216), MYOF (SEQ ID NO: 211), LAPTM4B (SEQ ID NO: 212), CALD1 (SEQ ID NO: 213), PDGFC (SEQ ID NO: 214), BASP1 (SEQ ID NO: 215), ID1 (SEQ ID NO: 217), and GJA1 (SEQ ID NO: 218)) and one or more biomarkers of resistance (e.g., one or more of IGLC1 (SEQ ID NO: 301, 302, 303, or 318), LAPTM5 (SEQ ID NO: 304 or 338), ARHGDIB (SEQ ID NO: 305 or 311), SLC43A3 (SEQ ID NO: 307), LCP1 (SEQ ID NO: 308), HCLS1 (SEQ ID NO: 309), CD53 (SEQ ID NO: 310), MZB1 (SEQ ID NO: 313), RASSF5 (SEQ ID NO: 314 or 386), FAM46C (SEQ ID NO: 315), RCSD1 (SEQ ID NO: 316), IGJ (SEQ ID NO: 317), LPXN (SEQ ID NO: 319), ITGB7 (SEQ ID NO: 320), and GTSF1 (SEQ ID NO: 321)) may be used in combination to determine the responsiveness of a cancer patient (e.g., a patient having cancer that is resistant to one or more cancer therapies other than irifolven) to treatment with irifolven. For example, the predicted responsiveness of a cancer patient may be determined from, e.g., the difference score, which may be defined as the difference between the mean of the expression level of the one or more biomarkers of sensitivity of Tables 1 and 3 and the mean of the expression level of the one or more biomarkers of resistance of Tables 2 and 4.

The difference score of the cancer patient can then be compared to the difference score based on the expression level of the biomarkers in a cell (e.g., a cancer cell) or tissue (e.g., a tumor tissue) known to be sensitive or resistant to treatment with irifolven. In particular, the patient may be responsive to treatment with irifolven if the difference score is substantially similar to the expression level of the biomarkers in a cell or tissue known to be sensitive to treatment

with irifolven. Alternatively, the patient may be non-responsive to treatment with irifolven if the difference score is substantially similar to the expression level of the biomarkers in a cell or tissue known to be resistant to treatment with irifolven. Additionally, the patient may be responsive to treatment with irifolven if the difference score is substantially similar to the expression level of the biomarkers in a cell or tissue known to be sensitive to treatment with irifolven than a cell or tissue known to be resistant to treatment with irifolven. Alternatively, the patient may be non-responsive to treatment with irifolven if the difference score is substantially similar to the expression level of the biomarkers in a cell or tissue known to be resistant to treatment with irifolven than a cell or tissue known to be sensitive to treatment with irifolven.

One or more biomarkers of sensitivity and/or resistance, identified as described herein, can be used to predict responsiveness to irifolven by measuring the expression level of the biomarkers in a biological sample obtained from the cancer patient. A single biomarker (e.g., any of the biomarkers of Tables 1-4, such as ATP1B1 (SEQ ID NO: 201)) may be used to determine the responsiveness of a cancer patient (e.g., a patient having cancer that is resistant to one or more cancer therapies other than irifolven) to irifolven. After determining the expression level of the biomarker(s) in a sample (e.g., a tumor sample) from the cancer patient, the expression level of the biomarker(s) in the sample may be compared to the expression level of the biomarker(s) in a cell (e.g., a cancer cell) or tissue (e.g., a tumor tissue) known to be sensitive to treatment with irifolven. If the expression level of the biomarker(s) in the sample from the cancer patient corresponds to (e.g., is identical to or has the same trend of expression level as) the expression level of the biomarker(s) in the cell or tissue known to be sensitive to irifolven, then the cancer patient is predicted to be responsive to treatment with irifolven. Alternatively, if the expression level of the biomarker(s) in the sample from the cancer patient is substantially dissimilar to the expression level of the biomarker(s) in the cell or tissue known to be sensitive to irifolven, then the cancer patient is predicted to be non-responsive to treatment with irifolven.

The expression level of the biomarker (e.g., ATP1B1 (SEQ ID NO: 201)) in a sample from the cancer patient may also be compared to the expression level of the biomarker in a cell (e.g., a cancer cell) or tissue (e.g., a tumor tissue) known to be resistant to treatment with irifolven. If the expression level of the biomarker in the sample from the cancer patient corresponds to the expression level of the biomarker in the cell or tissue known to be resistant to irifolven, then the cancer patient is predicted to be non-responsive to treatment with irifolven. Alternatively, if the expression level of the biomarker in the sample from the cancer patient is substantially dissimilar to the expression level of the biomarker in the cell or tissue known to be resistant to irifolven, then the cancer patient is predicted to be responsive to treatment with irifolven.

The responsiveness of a cancer patient (e.g., a patient having cancer that is resistant to one or more cancer therapies other than irifolven) to irifolven can also be predicted by comparing the expression level of a biomarker (e.g., ATP1B1 (SEQ ID NO: 201)) to the expression level of the biomarker in one or more cells or tissues (e.g., from a cancer patient population) known to be sensitive to treatment with irifolven and one or more cells or tissues (e.g., from a cancer patient population) known to be resistant to treatment with irifolven. In particular, the patient may be responsive to treatment with irifolven if the expression level of the

biomarker(s) corresponds to the expression level of the biomarker(s) in a cell or tissue known to be sensitive to treatment with irifolven relative to the expression level of the biomarkers in a cell or tissue known to be resistant to treatment with irifolven. Alternatively, the patient may be non-responsive to treatment with irifolven if the expression level of the biomarker(s) corresponds to the expression level of the biomarker(s) in a cell or tissue known to be resistant to treatment with irifolven relative to the expression level of the biomarkers in a cell or tissue known to be resistant to treatment with irifolven.

Additionally, one or more biomarkers of sensitivity (e.g., one or more of ATP1B1 (SEQ ID NO: 201 or 219), UCHL1 (SEQ ID NO: 202), PTGR1 (SEQ ID NO: 203 or 210), NME7 (SEQ ID NO: 204), PLS3 (SEQ ID NO: 205), S100A10 (SEQ ID NO: 206), CD24 (SEQ ID NO: 207, 209, or 220), NQO1 (SEQ ID NO: 208 or 216), MYOF (SEQ ID NO: 211), LAPTM4B (SEQ ID NO: 212), CALD1 (SEQ ID NO: 213), PDGFC (SEQ ID NO: 214), BASP1 (SEQ ID NO: 215), ID1 (SEQ ID NO: 217), and GJA1 (SEQ ID NO: 218)) and one or more biomarkers of resistance (e.g., one or more of IGLC1 (SEQ ID NO: 301, 302, 303, or 318), LAPTM5 (SEQ ID NO: 304 or 338), ARHGDIB (SEQ ID NO: 305 or 311), SLC43A3 (SEQ ID NO: 307), LCP1 (SEQ ID NO: 308), HCLS1 (SEQ ID NO: 309), CD53 (SEQ ID NO: 310), MZB1 (SEQ ID NO: 313), RASSF5 (SEQ ID NO: 314 or 386), FAM46C (SEQ ID NO: 315), RCSD1 (SEQ ID NO: 316), IGJ (SEQ ID NO: 317), LPXN (SEQ ID NO: 319), ITGB7 (SEQ ID NO: 320), and GTSF1 (SEQ ID NO: 321)) may be used in combination to determine the responsiveness of a cancer patient (e.g., a patient having cancer that is resistant to one or more cancer therapies other than irifolven) to treatment with irifolven. For example, the predicted responsiveness of a cancer patient may be determined from, e.g., the difference score, which may be defined as the difference between the mean of the expression level of the one or more biomarkers of sensitivity of Tables 1 and 3 and the mean of the expression level of the one or more biomarkers of resistance of Tables 2 and 4.

The difference score of the cancer patient can then be compared to the difference score based on the expression level of the biomarkers in a cell (e.g., a cancer cell) or tissue (e.g., a tumor tissue) known to be sensitive or resistant to treatment with irifolven. In particular, the patient may be responsive to treatment with irifolven if the difference score corresponds to the expression level of the biomarkers in a cell or tissue known to be sensitive to treatment with irifolven. Alternatively, the patient may be non-responsive to treatment with irifolven if the difference score corresponds to the expression level of the biomarkers in a cell or tissue known to be resistant to treatment with irifolven. Additionally, the patient may be responsive to treatment with irifolven if the difference score corresponds to the expression level of the biomarkers in a cell or tissue known to be sensitive to treatment with irifolven relative to the expression level of the biomarkers in a cell or tissue known to be resistant to treatment with irifolven. Alternatively, the patient may be non-responsive to treatment with irifolven if the difference score corresponds to the expression level of the biomarkers in a cell or tissue known to be resistant to treatment with irifolven relative to the expression level of the biomarkers in a cell or tissue known to be sensitive to treatment with irifolven.

Preferably, the cell or tissue known to be either sensitive or resistant to irifolven is of the same cancer type as the cancer patient with an unknown responsiveness to irifolven. For example, the cancer patient and the cell or tissue known

to be either sensitive or resistant to irifolven may both have a cancer type selected from a solid tumor or a hematological cancer, e.g., prostate cancer, ovarian cancer (e.g., ovarian adenocarcinoma or embryonal carcinoma), liver cancer (e.g., hepatocellular carcinoma (HCC) or hepatoma), myeloma (e.g., multiple myeloma), colorectal cancer (e.g., colon cancer and rectal cancer), leukemia (e.g., acute myeloid leukemia, acute lymphoid leukemia, chronic myeloid leukemia, chronic lymphocytic leukemia, acute myeloblastic leukemia, acute promyelocytic leukemia, acute myelomonocytic leukemia, acute monocytic leukemia, acute erythroleukemia, and chronic leukemia), myelodysplastic syndrome, lymphoma (e.g., diffuse large B-cell lymphoma, cutaneous T-cell lymphoma, peripheral T-cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, Waldenstrom's macroglobulinemia, and lymphocytic lymphoma), cervical cancer, esophageal cancer, melanoma, glioma (e.g., oligodendroglioma), pancreatic cancer (e.g., adenocarcinoma, signet ring cell carcinoma, hepatoid carcinoma, colloid carcinoma, islet cell carcinoma, and pancreatic neuroendocrine carcinoma), gastrointestinal stromal tumor, sarcoma (e.g., fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, leiomyosarcoma, Ewing's sarcoma, and rhabdomyosarcoma), breast cancer (e.g., medullary carcinoma), ER-positive cancer, bladder cancer, head and neck cancer (e.g., squamous cell carcinoma of the head and neck), lung cancer (e.g., non-small cell lung carcinoma, large cell carcinoma, bronchogenic carcinoma, and papillary adenocarcinoma), metastatic cancer, oral cavity cancer, uterine cancer, testicular cancer (e.g., seminoma and embryonal carcinoma), skin cancer (e.g., squamous cell carcinoma and basal cell carcinoma), thyroid cancer (e.g., papillary carcinoma and medullary carcinoma), brain cancer (e.g., astrocytoma and craniopharyngioma), stomach cancer, intraepithelial cancer, bone cancer, biliary tract cancer, eye cancer, larynx cancer, kidney cancer (e.g., renal cell carcinoma and Wilms tumor), gastric cancer, blastoma (e.g., nephroblastoma, medulloblastoma, hemangioblastoma, neuroblastoma, and retinoblastoma), polycythemia vera, chordoma, synovioma, mesothelioma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, cystadenocarcinoma, bile duct carcinoma, choriocarcinoma, epithelial carcinoma, ependymoma, pinealoma, acoustic neuroma, schwannoma, meningioma, pituitary adenoma, nerve sheath tumor, cancer of the small intestine, cancer of the endocrine system, cancer of the penis, cancer of the urethra, cutaneous or intraocular melanoma, a gynecologic tumor, solid tumors of childhood, and neoplasms of the central nervous system. In particular, the cancer of the patient and the cell or tissue with known resistance or sensitivity to irifolven is, e.g., prostate cancer, ovarian cancer, hepatocellular carcinoma (HCC), multiple myeloma, breast cancer, acute myelogenous leukemia (AML), acute lympho-blastic leukemia (ALL), chronic lymphocytic leukemia (CLL), myelodysplastic syndrome (MDS), chronic myelogenous leukemia-chronic phase (CMLCP), diffuse large B-cell lymphoma (DLBCL), cutaneous T-cell lymphoma (CTCL), peripheral T-cell lymphoma (PTCL), Hodgkin's lymphoma, cervical cancer, renal cell carcinoma (RCC), esophageal cancer, melanoma, glioma, pancreatic cancer, gastrointestinal stromal tumors (GIST), sarcoma, estrogen receptor-positive (ERpos) breast cancer, non-small cell lung carcinoma (NSCLC), colon cancer, bladder cancer, or squamous cell carcinoma of the head and neck (SCCHN).

Machine learning techniques such as Neural Networks, Support Vector Machines, K Nearest Neighbor, and Nearest Centroids may also be employed to develop models that discriminate patients sensitive to treatment with irifolven from those resistant to treatment with irifolven using biomarker expression as model variables which assign each patient a classification as sensitive or resistant to treatment with irifolven. Machine learning techniques used to classify patients using various measurements are described in U.S. Pat. No. 5,822,715; U.S. Patent Application Publication Nos. 2003/0073083, 2005/0227266, 2005/0208512, 2005/0123945, 2003/0129629, and 2002/0006613; and in Vapnik V N. Statistical Learning Theory, John Wiley & Sons, New York, 1998; Hastie et al., 2001, The Elements of Statistical Learning: Data Mining, Inference, and Prediction, Springer, N.Y.; Agresti, 1996, An Introduction to Categorical Data Analysis, John Wiley & Sons, New York; V. Tresp et al., "Neural Network Modeling of Physiological Processes," in Hanson S. J. et al. (Eds.), Computational Learning Theory and Natural Learning Systems 2, MIT Press, 1994, each of which are hereby incorporated by reference in their entirety. Biomarkers of Sensitivity and Resistance

The expression levels of one or more biomarkers of Tables 1-4 can be used to determine cancer patient responsiveness to treatment with irifolven. Once determined to be responsive, the patient can be treated with irifolven. In particular, the biomarker ATP1B1 (SEQ ID NO: 201 or 219) may be used to assess a cancer patient's (e.g., a patient having cancer that is resistant to one or more cancer therapies other than irifolven) responsiveness to irifolven. The expression level of the biomarker ATP1B1 (SEQ ID NO: 201 or 219) may be assessed using nucleic acid amplification methods (e.g., PCR) or a device (e.g., a microarray). As is described above, the expression level of ATP1B1 (SEQ ID NO: 201 or 219) in the patient sample may then be compared, e.g., to the expression level of ATP1B1 (SEQ ID NO: 201 or 219) in a cell (e.g., a cancer cell) or tissue (e.g., a tumor tissue) known to be sensitive or resistant to treatment with irifolven and used to determine the cancer patient's responsiveness to irifolven. The biomarker ATP1B1 (SEQ ID NO: 201 or 219) may be used alone to predict cancer patient responsiveness to treatment with irifolven or in combination with one or more additional biomarkers (e.g., one, two, three, four, five, ten, or all of the biomarkers shown in Tables 1-4), such as UCHL1 (SEQ ID NO: 202), PTGR1 (SEQ ID NO: 203 or 210), NME7 (SEQ ID NO: 204), PLS3 (SEQ ID NO: 205), S100A10 (SEQ ID NO: 206), CD24 (SEQ ID NO: 207, 209, or 220), NQO1 (SEQ ID NO: 208 or 216), MYOF (SEQ ID NO: 211), LAPTM4B (SEQ ID NO: 212), CALD1 (SEQ ID NO: 213), PDGFC (SEQ ID NO: 214), BASP1 (SEQ ID NO: 215), ID1 (SEQ ID NO: 217), GJA1 (SEQ ID NO: 218), IGLC1 (SEQ ID NO: 301, 302, 303, or 318), LAPTM5 (SEQ ID NO: 304 or 338), ARHGDIB (SEQ ID NO: 305 or 311), SLC43A3 (SEQ ID NO: 307), LCP1 (SEQ ID NO: 308), HCLS1 (SEQ ID NO: 309), CD53 (SEQ ID NO: 310), MZB1 (SEQ ID NO: 313), RASSF5 (SEQ ID NO: 314 or 386), FAM46C (SEQ ID NO: 315), RCSD1 (SEQ ID NO: 316), IGJ (SEQ ID NO: 317), LPXN (SEQ ID NO: 319), ITGB7 (SEQ ID NO: 320), and/or GTSF1 (SEQ ID NO: 321). The expression level of the biomarker(s) may be determined using, e.g., a microarray, PCR, or other techniques described herein, for example, using a nucleic acid probe sequence based on the target sequences shown in Tables 1-4.

The expression level of the biomarker UCHL1 (SEQ ID NO: 202) may be assessed using nucleic acid amplification methods (e.g., PCR) or a device (e.g., a microarray). As is

described above, the expression level of UCHL1 (SEQ ID NO: 202) in the patient sample may then be compared, e.g., to the expression level of UCHL1 (SEQ ID NO: 202) in a cell (e.g., a cancer cell) or tissue (e.g., a tumor tissue) known to be sensitive or resistant to treatment with irifolven and used to determine the cancer patient's responsiveness to irifolven. The biomarker UCHL1 (SEQ ID NO: 202) may be used alone to predict cancer patient responsiveness to treatment with irifolven or in combination with one or more additional biomarkers (e.g., one, two, three, four, five, ten, or all of the biomarkers shown in Tables 1-4), such as ATP1B1 (SEQ ID NO: 201 or 219), PTGR1 (SEQ ID NO: 203 or 210), NME7 (SEQ ID NO: 204), PLS3 (SEQ ID NO: 205), S100A10 (SEQ ID NO: 206), CD24 (SEQ ID NO: 207, 209, or 220), NQO1 (SEQ ID NO: 208 or 216), MYOF (SEQ ID NO: 211), LAPTM4B (SEQ ID NO: 212), CALD1 (SEQ ID NO: 213), PDGFC (SEQ ID NO: 214), BASP1 (SEQ ID NO: 215), ID1 (SEQ ID NO: 217), GJA1 (SEQ ID NO: 218), IGLC1 (SEQ ID NO: 301, 302, 303, or 318), LAPTM5 (SEQ ID NO: 304 or 338), ARHGDIB (SEQ ID NO: 305 or 311), SLC43A3 (SEQ ID NO: 307), LCP1 (SEQ ID NO: 308), HCLS1 (SEQ ID NO: 309), CD53 (SEQ ID NO: 310), MZB1 (SEQ ID NO: 313), RASSF5 (SEQ ID NO: 314 or 386), FAM46C (SEQ ID NO: 315), RCSD1 (SEQ ID NO: 316), IGJ (SEQ ID NO: 317), LPXN (SEQ ID NO: 319), ITGB7 (SEQ ID NO: 320), and/or GTSF1 (SEQ ID NO: 321). The expression level of the biomarker(s) may be determined using, e.g., a microarray, PCR, or other techniques described herein, for example, using a nucleic acid probe sequence based on the target sequences shown in Tables 1-4.

The biomarker PTGR1 (SEQ ID NO: 203 or 210) may be used to assess a cancer patient's (e.g., a patient having cancer that is resistant to one or more cancer therapies other than irifolven) responsiveness to irifolven. The expression level of the biomarker PTGR1 (SEQ ID NO: 203 or 210) may be assessed using nucleic acid amplification methods (e.g., PCR) or a device (e.g., a microarray). As is described above, the expression level of PTGR1 (SEQ ID NO: 203 or 210) in the patient sample may then be compared, e.g., to the expression level of PTGR1 (SEQ ID NO: 203 or 210) in a cell (e.g., a cancer cell) or tissue (e.g., a tumor tissue) known to be sensitive or resistant to treatment with irifolven and used to determine the cancer patient's responsiveness to irifolven. The biomarker PTGR1 (SEQ ID NO: 203 or 210) may be used alone to predict cancer patient responsiveness to treatment with irifolven or in combination with one or more additional biomarkers (e.g., one, two, three, four, five, ten, or all of the biomarkers shown in Tables 1-4), such as ATP1B1 (SEQ ID NO: 201 or 219), UCHL1 (SEQ ID NO: 202), NME7 (SEQ ID NO: 204), PLS3 (SEQ ID NO: 205), S100A10 (SEQ ID NO: 206), CD24 (SEQ ID NO: 207, 209, or 220), NQO1 (SEQ ID NO: 208 or 216), MYOF (SEQ ID NO: 211), LAPTM4B (SEQ ID NO: 212), CALD1 (SEQ ID NO: 213), PDGFC (SEQ ID NO: 214), BASP1 (SEQ ID NO: 215), ID1 (SEQ ID NO: 217), GJA1 (SEQ ID NO: 218), IGLC1 (SEQ ID NO: 301, 302, 303, or 318), LAPTM5 (SEQ ID NO: 304 or 338), ARHGDIB (SEQ ID NO: 305 or 311), SLC43A3 (SEQ ID NO: 307), LCP1 (SEQ ID NO: 308), HCLS1 (SEQ ID NO: 309), CD53 (SEQ ID NO: 310), MZB1 (SEQ ID NO: 313), RASSF5 (SEQ ID NO: 314 or 386), FAM46C (SEQ ID NO: 315), RCSD1 (SEQ ID NO: 316), IGJ (SEQ ID NO: 317), LPXN (SEQ ID NO: 319), ITGB7 (SEQ ID NO: 320), and/or GTSF1 (SEQ ID NO: 321). The expression level of the biomarker(s) may be determined using, e.g., a microarray, PCR, or other tech-

niques described herein, for example, using a nucleic acid probe sequence based on the target sequences shown in Tables 1-4.

The biomarker NME7 (SEQ ID NO: 204) may be used to assess a cancer patient's (e.g., a patient having cancer that is resistant to one or more cancer therapies other than irifolven) responsiveness to irifolven. The expression level of the biomarker NME7 (SEQ ID NO: 204) may be assessed using nucleic acid amplification methods (e.g., PCR) or a device (e.g., a microarray). As is described above, the expression level of NME7 (SEQ ID NO: 204) in the patient sample may then be compared, e.g., to the expression level of NME7 (SEQ ID NO: 204) in a cell (e.g., a cancer cell) or tissue (e.g., a tumor tissue) known to be sensitive or resistant to treatment with irifolven and used to determine the cancer patient's responsiveness to irifolven. The biomarker NME7 (SEQ ID NO: 204) may be used alone to predict cancer patient responsiveness to treatment with irifolven or in combination with one or more additional biomarkers (e.g., one, two, three, four, five, ten, or all of the biomarkers shown in Tables 1-4), such as ATP1B1 (SEQ ID NO: 201 or 219), UCHL1 (SEQ ID NO: 202), PTGR1 (SEQ ID NO: 203 or 210), PLS3 (SEQ ID NO: 205), S100A10 (SEQ ID NO: 206), CD24 (SEQ ID NO: 207, 209, or 220), NQO1 (SEQ ID NO: 208 or 216), MYOF (SEQ ID NO: 211), LAPTM4B (SEQ ID NO: 212), CALD1 (SEQ ID NO: 213), PDGFC (SEQ ID NO: 214), BASP1 (SEQ ID NO: 215), ID1 (SEQ ID NO: 217), GJA1 (SEQ ID NO: 218), IGLC1 (SEQ ID NO: 301, 302, 303, or 318), LAPTM5 (SEQ ID NO: 304 or 338), ARHGDIB (SEQ ID NO: 305 or 311), SLC43A3 (SEQ ID NO: 307), LCP1 (SEQ ID NO: 308), HCLS1 (SEQ ID NO: 309), CD53 (SEQ ID NO: 310), MZB1 (SEQ ID NO: 313), RASSF5 (SEQ ID NO: 314 or 386), FAM46C (SEQ ID NO: 315), RCSD1 (SEQ ID NO: 316), IGJ (SEQ ID NO: 317), LPXN (SEQ ID NO: 319), ITGB7 (SEQ ID NO: 320), and/or GTSF1 (SEQ ID NO: 321). The expression level of the biomarker(s) may be determined using, e.g., a microarray, PCR, or other techniques described herein, for example, using a nucleic acid probe sequence based on the target sequences shown in Tables 1-4.

The biomarker PLS3 (SEQ ID NO: 205) may be used to assess a cancer patient's (e.g., a patient having cancer that is resistant to one or more cancer therapies other than irifolven) responsiveness to irifolven. The expression level of the biomarker PLS3 (SEQ ID NO: 205) may be assessed using nucleic acid amplification methods (e.g., PCR) or a device (e.g., a microarray). As is described above, the expression level of PLS3 (SEQ ID NO: 205) in the patient sample may then be compared, e.g., to the expression level of PLS3 (SEQ ID NO: 205) in a cell (e.g., a cancer cell) or tissue (e.g., a tumor tissue) known to be sensitive or resistant to treatment with irifolven and used to determine the cancer patient's responsiveness to irifolven. The biomarker PLS3 (SEQ ID NO: 205) may be used alone to predict cancer patient responsiveness to treatment with irifolven or in combination with one or more additional biomarkers (e.g., one, two, three, four, five, ten, or all of the biomarkers shown in Tables 1-4), such as ATP1B1 (SEQ ID NO: 201 or 219), UCHL1 (SEQ ID NO: 202), PTGR1 (SEQ ID NO: 203 or 210), NME7 (SEQ ID NO: 204), S100A10 (SEQ ID NO: 206), CD24 (SEQ ID NO: 207, 209, or 220), NQO1 (SEQ ID NO: 208 or 216), MYOF (SEQ ID NO: 211), LAPTM4B (SEQ ID NO: 212), CALD1 (SEQ ID NO: 213), PDGFC (SEQ ID NO: 214), BASP1 (SEQ ID NO: 215), ID1 (SEQ ID NO: 217), GJA1 (SEQ ID NO: 218), IGLC1 (SEQ ID NO: 301, 302, 303, or 318), LAPTM5 (SEQ ID NO: 304 or 338), ARHGDIB (SEQ ID NO: 305 or 311), SLC43A3

(SEQ ID NO: 307), LCP1 (SEQ ID NO: 308), HCLS1 (SEQ ID NO: 309), CD53 (SEQ ID NO: 310), MZB1 (SEQ ID NO: 313), RASSF5 (SEQ ID NO: 314 or 386), FAM46C (SEQ ID NO: 315), RCSD1 (SEQ ID NO: 316), IGJ (SEQ ID NO: 317), LPXN (SEQ ID NO: 319), ITGB7 (SEQ ID NO: 320), and/or GTSF1 (SEQ ID NO: 321). The expression level of the biomarker(s) may be determined using, e.g., a microarray, PCR, or other techniques described herein, for example, using a nucleic acid probe sequence based on the target sequences shown in Tables 1-4.

The biomarker S100A10 (SEQ ID NO: 206) may be used to assess a cancer patient's (e.g., a patient having cancer that is resistant to one or more cancer therapies other than irifolven) responsiveness to irifolven. The expression level of the biomarker S100A10 (SEQ ID NO: 206) may be assessed using nucleic acid amplification methods (e.g., PCR) or a device (e.g., a microarray). As is described above, the expression level of S100A10 (SEQ ID NO: 206) in the patient sample may then be compared, e.g., to the expression level of S100A10 (SEQ ID NO: 206) in a cell (e.g., a cancer cell) or tissue (e.g., a tumor tissue) known to be sensitive or resistant to treatment with irifolven and used to determine the cancer patient's responsiveness to irifolven. The biomarker S100A10 (SEQ ID NO: 206) may be used alone to predict cancer patient responsiveness to treatment with irifolven or in combination with one or more additional biomarkers (e.g., one, two, three, four, five, ten, or all of the biomarkers shown in Tables 1-4), such as ATP1B1 (SEQ ID NO: 201 or 219), UCHL1 (SEQ ID NO: 202), PTGR1 (SEQ ID NO: 203 or 210), NME7 (SEQ ID NO: 204), PLS3 (SEQ ID NO: 205), CD24 (SEQ ID NO: 207, 209, or 220), NQO1 (SEQ ID NO: 208 or 216), MYOF (SEQ ID NO: 211), LAPTM4B (SEQ ID NO: 212), CALD1 (SEQ ID NO: 213), PDGFC (SEQ ID NO: 214), BASP1 (SEQ ID NO: 215), ID1 (SEQ ID NO: 217), GJA1 (SEQ ID NO: 218), IGLC1 (SEQ ID NO: 301, 302, 303, or 318), LAPTM5 (SEQ ID NO: 304 or 338), ARHGDIB (SEQ ID NO: 305 or 311), SLC43A3 (SEQ ID NO: 307), LCP1 (SEQ ID NO: 308), HCLS1 (SEQ ID NO: 309), CD53 (SEQ ID NO: 310), MZB1 (SEQ ID NO: 313), RASSF5 (SEQ ID NO: 314 or 386), FAM46C (SEQ ID NO: 315), RCSD1 (SEQ ID NO: 316), IGJ (SEQ ID NO: 317), LPXN (SEQ ID NO: 319), ITGB7 (SEQ ID NO: 320), and/or GTSF1 (SEQ ID NO: 321). The expression level of the biomarker(s) may be determined using, e.g., a microarray, PCR, or other techniques described herein, for example, using a nucleic acid probe sequence based on the target sequences shown in Tables 1-4.

The biomarker CD24 (SEQ ID NO: 207, 209, or 220) may be used to assess a cancer patient's (e.g., a patient having cancer that is resistant to one or more cancer therapies other than irifolven) responsiveness to irifolven. The expression level of the biomarker CD24 (SEQ ID NO: 207, 209, or 220) may be assessed using nucleic acid amplification methods (e.g., PCR) or a device (e.g., a microarray). As is described above, the expression level of CD24 (SEQ ID NO: 207, 209, or 220) in the patient sample may then be compared, e.g., to the expression level of CD24 (SEQ ID NO: 207, 209, or 220) in a cell (e.g., a cancer cell) or tissue (e.g., a tumor tissue) known to be sensitive or resistant to treatment with irifolven and used to determine the cancer patient's responsiveness to irifolven. The biomarker CD24 (SEQ ID NO: 207, 209, or 220) may be used alone to predict cancer patient responsiveness to treatment with irifolven or in combination with one or more additional biomarkers (e.g., one, two, three, four, five, ten, or all of the biomarkers shown in Tables 1-4), such as ATP1B1 (SEQ ID NO: 201 or 219), UCHL1 (SEQ ID NO: 202), PTGR1 (SEQ ID NO: 203 or 210),

NME7 (SEQ ID NO: 204), PLS3 (SEQ ID NO: 205), S100A10 (SEQ ID NO: 206), NQO1 (SEQ ID NO: 208 or 216), MYOF (SEQ ID NO: 211), LAPTM4B (SEQ ID NO: 212), CALD1 (SEQ ID NO: 213), PDGFC (SEQ ID NO: 214), BASP1 (SEQ ID NO: 215), ID1 (SEQ ID NO: 217), GJA1 (SEQ ID NO: 218), IGLC1 (SEQ ID NO: 301, 302, 303, or 318), LAPTM5 (SEQ ID NO: 304 or 338), ARHGDIB (SEQ ID NO: 305 or 311), SLC43A3 (SEQ ID NO: 307), LCP1 (SEQ ID NO: 308), HCLS1 (SEQ ID NO: 309), CD53 (SEQ ID NO: 310), MZB1 (SEQ ID NO: 313), RASSF5 (SEQ ID NO: 314 or 386), FAM46C (SEQ ID NO: 315), RCSD1 (SEQ ID NO: 316), IGJ (SEQ ID NO: 317), LPXN (SEQ ID NO: 319), ITGB7 (SEQ ID NO: 320), and/or GTSF1 (SEQ ID NO: 321). The expression level of the biomarker(s) may be determined using, e.g., a microarray, PCR, or other techniques described herein, for example, using a nucleic acid probe sequence based on the target sequences shown in Tables 1-4.

The biomarker NQO1 (SEQ ID NO: 208 or 216) may be used to assess a cancer patient's (e.g., a patient having cancer that is resistant to one or more cancer therapies other than irifolven) responsiveness to irifolven. The expression level of the biomarker NQO1 (SEQ ID NO: 208 or 216) may be assessed using nucleic acid amplification methods (e.g., PCR) or a device (e.g., a microarray). As is described above, the expression level of NQO1 (SEQ ID NO: 208 or 216) in the patient sample may then be compared, e.g., to the expression level of NQO1 (SEQ ID NO: 208 or 216) in a cell (e.g., a cancer cell) or tissue (e.g., a tumor tissue) known to be sensitive or resistant to treatment with irifolven and used to determine the cancer patient's responsiveness to irifolven. The biomarker NQO1 (SEQ ID NO: 208 or 216) may be used alone to predict cancer patient responsiveness to treatment with irifolven or in combination with one or more additional biomarkers (e.g., one, two, three, four, five, ten, or all of the biomarkers shown in Tables 1-4), such as ATP1B1 (SEQ ID NO: 201 or 219), UCHL1 (SEQ ID NO: 202), PTGR1 (SEQ ID NO: 203 or 210), NME7 (SEQ ID NO: 204), PLS3 (SEQ ID NO: 205), S100A10 (SEQ ID NO: 206), MYOF (SEQ ID NO: 211), LAPTM4B (SEQ ID NO: 212), CALD1 (SEQ ID NO: 213), PDGFC (SEQ ID NO: 214), BASP1 (SEQ ID NO: 215), ID1 (SEQ ID NO: 217), GJA1 (SEQ ID NO: 218), IGLC1 (SEQ ID NO: 301, 302, 303, or 318), LAPTM5 (SEQ ID NO: 304 or 338), ARHGDIB (SEQ ID NO: 305 or 311), SLC43A3 (SEQ ID NO: 307), LCP1 (SEQ ID NO: 308), HCLS1 (SEQ ID NO: 309), CD53 (SEQ ID NO: 310), MZB1 (SEQ ID NO: 313), RASSF5 (SEQ ID NO: 314 or 386), FAM46C (SEQ ID NO: 315), RCSD1 (SEQ ID NO: 316), IGJ (SEQ ID NO: 317), LPXN (SEQ ID NO: 319), ITGB7 (SEQ ID NO: 320), and/or GTSF1 (SEQ ID NO: 321). The expression level of the biomarker(s) may be determined using, e.g., a microarray, PCR, or other techniques described herein, for example, using a nucleic acid probe sequence based on the target sequences shown in Tables 1-4.

The expression levels of one or more biomarkers of Tables 1-4 can be used to determine cancer patient responsiveness to treatment with irifolven. Once determined to be responsive, the patient can be treated with irifolven. In particular, the biomarker MYOF (SEQ ID NO: 211) may be used to assess a cancer patient's (e.g., a patient having cancer that is resistant to one or more cancer therapies other than irifolven) responsiveness to irifolven. The expression level of the biomarker MYOF (SEQ ID NO: 211) may be assessed using nucleic acid amplification methods (e.g., PCR) or a device (e.g., a microarray). As is described above, the expression level of MYOF (SEQ ID NO: 211) in the patient

sample may then be compared, e.g., to the expression level of MYOF (SEQ ID NO: 211) in a cell (e.g., a cancer cell) or tissue (e.g., a tumor tissue) known to be sensitive or resistant to treatment with irifolven and used to determine the cancer patient's responsiveness to irifolven. The biomarker MYOF (SEQ ID NO: 211) may be used alone to predict cancer patient responsiveness to treatment with irifolven or in combination with one or more additional biomarkers (e.g., one, two, three, four, five, ten, or all of the biomarkers shown in Tables 1-4), such as ATP1B1 (SEQ ID NO: 201 or 219), UCHL1 (SEQ ID NO: 202), PTGR1 (SEQ ID NO: 203 or 210), NME7 (SEQ ID NO: 204), PLS3 (SEQ ID NO: 205), S100A10 (SEQ ID NO: 206), CD24 (SEQ ID NO: 207, 209, or 220), NQO1 (SEQ ID NO: 208 or 216), LAPT4B (SEQ ID NO: 212), CALD1 (SEQ ID NO: 213), PDGFC (SEQ ID NO: 214), BASP1 (SEQ ID NO: 215), ID1 (SEQ ID NO: 217), GJA1 (SEQ ID NO: 218), IGLC1 (SEQ ID NO: 301, 302, 303, or 318), LAPT5 (SEQ ID NO: 304 or 338), ARHGDIB (SEQ ID NO: 305 or 311), SLC43A3 (SEQ ID NO: 307), LCP1 (SEQ ID NO: 308), HCLS1 (SEQ ID NO: 309), CD53 (SEQ ID NO: 310), MZB1 (SEQ ID NO: 313), RASSF5 (SEQ ID NO: 314 or 386), FAM46C (SEQ ID NO: 315), RCSD1 (SEQ ID NO: 316), IGJ (SEQ ID NO: 317), LPXN (SEQ ID NO: 319), ITGB7 (SEQ ID NO: 320), and/or GTSF1 (SEQ ID NO: 321). The expression level of the biomarker(s) may be determined using, e.g., a microarray, PCR, or other techniques described herein, for example, using a nucleic acid probe sequence based on the target sequences shown in Tables 1-4.

The biomarker LAPT4B (SEQ ID NO: 212) may be used to assess a cancer patient's (e.g., a patient having cancer that is resistant to one or more cancer therapies other than irifolven) responsiveness to irifolven. The expression level of the biomarker LAPT4B (SEQ ID NO: 212) may be assessed using nucleic acid amplification methods (e.g., PCR) or a device (e.g., a microarray). As is described above, the expression level of LAPT4B (SEQ ID NO: 212) in the patient sample may then be compared, e.g., to the expression level of LAPT4B (SEQ ID NO: 212) in a cell (e.g., a cancer cell) or tissue (e.g., a tumor tissue) known to be sensitive or resistant to treatment with irifolven and used to determine the cancer patient's responsiveness to irifolven. The biomarker LAPT4B (SEQ ID NO: 212) may be used alone to predict cancer patient responsiveness to treatment with irifolven or in combination with one or more additional biomarkers (e.g., one, two, three, four, five, ten, or all of the biomarkers shown in Tables 1-4), such as ATP1B1 (SEQ ID NO: 201 or 219), UCHL1 (SEQ ID NO: 202), PTGR1 (SEQ ID NO: 203 or 210), NME7 (SEQ ID NO: 204), PLS3 (SEQ ID NO: 205), S100A10 (SEQ ID NO: 206), CD24 (SEQ ID NO: 207, 209, or 220), NQO1 (SEQ ID NO: 208 or 216), MYOF (SEQ ID NO: 211), CALD1 (SEQ ID NO: 213), PDGFC (SEQ ID NO: 214), BASP1 (SEQ ID NO: 215), ID1 (SEQ ID NO: 217), GJA1 (SEQ ID NO: 218), IGLC1 (SEQ ID NO: 301, 302, 303, or 318), LAPT5 (SEQ ID NO: 304 or 338), ARHGDIB (SEQ ID NO: 305 or 311), SLC43A3 (SEQ ID NO: 307), LCP1 (SEQ ID NO: 308), HCLS1 (SEQ ID NO: 309), CD53 (SEQ ID NO: 310), MZB1 (SEQ ID NO: 313), RASSF5 (SEQ ID NO: 314 or 386), FAM46C (SEQ ID NO: 315), RCSD1 (SEQ ID NO: 316), IGJ (SEQ ID NO: 317), LPXN (SEQ ID NO: 319), ITGB7 (SEQ ID NO: 320), and/or GTSF1 (SEQ ID NO: 321). The expression level of the biomarker(s) may be determined using, e.g., a microarray, PCR, or other techniques described herein, for example, using a nucleic acid probe sequence based on the target sequences shown in Tables 1-4.

The biomarker CALD1 (SEQ ID NO: 213) may be used to assess a cancer patient's (e.g., a patient having cancer that is resistant to one or more cancer therapies other than irifolven) responsiveness to irifolven. The expression level of the biomarker CALD1 (SEQ ID NO: 213) may be assessed using nucleic acid amplification methods (e.g., PCR) or a device (e.g., a microarray). As is described above, the expression level of CALD1 (SEQ ID NO: 213) in the patient sample may then be compared, e.g., to the expression level of CALD1 (SEQ ID NO: 213) in a cell (e.g., a cancer cell) or tissue (e.g., a tumor tissue) known to be sensitive or resistant to treatment with irifolven and used to determine the cancer patient's responsiveness to irifolven. The biomarker CALD1 (SEQ ID NO: 213) may be used alone to predict cancer patient responsiveness to treatment with irifolven or in combination with one or more additional biomarkers (e.g., one, two, three, four, five, ten, or all of the biomarkers shown in Tables 1-4), such as ATP1B1 (SEQ ID NO: 201 or 219), UCHL1 (SEQ ID NO: 202), PTGR1 (SEQ ID NO: 203 or 210), NME7 (SEQ ID NO: 204), PLS3 (SEQ ID NO: 205), S100A10 (SEQ ID NO: 206), CD24 (SEQ ID NO: 207, 209, or 220), NQO1 (SEQ ID NO: 208 or 216), MYOF (SEQ ID NO: 211), LAPT4B (SEQ ID NO: 212), PDGFC (SEQ ID NO: 214), BASP1 (SEQ ID NO: 215), ID1 (SEQ ID NO: 217), GJA1 (SEQ ID NO: 218), IGLC1 (SEQ ID NO: 301, 302, 303, or 318), LAPT5 (SEQ ID NO: 304 or 338), ARHGDIB (SEQ ID NO: 305 or 311), SLC43A3 (SEQ ID NO: 307), LCP1 (SEQ ID NO: 308), HCLS1 (SEQ ID NO: 309), CD53 (SEQ ID NO: 310), MZB1 (SEQ ID NO: 313), RASSF5 (SEQ ID NO: 314 or 386), FAM46C (SEQ ID NO: 315), RCSD1 (SEQ ID NO: 316), IGJ (SEQ ID NO: 317), LPXN (SEQ ID NO: 319), ITGB7 (SEQ ID NO: 320), and/or GTSF1 (SEQ ID NO: 321). The expression level of the biomarker(s) may be determined using, e.g., a microarray, PCR, or other techniques described herein, for example, using a nucleic acid probe sequence based on the target sequences shown in Tables 1-4.

The biomarker PDGFC (SEQ ID NO: 214) may be used to assess a cancer patient's (e.g., a patient having cancer that is resistant to one or more cancer therapies other than irifolven) responsiveness to irifolven. The expression level of the biomarker PDGFC (SEQ ID NO: 214) may be assessed using nucleic acid amplification methods (e.g., PCR) or a device (e.g., a microarray). As is described above, the expression level of PDGFC (SEQ ID NO: 214) in the patient sample may then be compared, e.g., to the expression level of PDGFC (SEQ ID NO: 214) in a cell (e.g., a cancer cell) or tissue (e.g., a tumor tissue) known to be sensitive or resistant to treatment with irifolven and used to determine the cancer patient's responsiveness to irifolven. The biomarker PDGFC (SEQ ID NO: 214) may be used alone to predict cancer patient responsiveness to treatment with irifolven or in combination with one or more additional biomarkers (e.g., one, two, three, four, five, ten, or all of the biomarkers shown in Tables 1-4), such as ATP1B1 (SEQ ID NO: 201 or 219), UCHL1 (SEQ ID NO: 202), PTGR1 (SEQ ID NO: 203 or 210), NME7 (SEQ ID NO: 204), PLS3 (SEQ ID NO: 205), S100A10 (SEQ ID NO: 206), CD24 (SEQ ID NO: 207, 209, or 220), NQO1 (SEQ ID NO: 208 or 216), MYOF (SEQ ID NO: 211), LAPT4B (SEQ ID NO: 212), CALD1 (SEQ ID NO: 213), BASP1 (SEQ ID NO: 215), ID1 (SEQ ID NO: 217), GJA1 (SEQ ID NO: 218), IGLC1 (SEQ ID NO: 301, 302, 303, or 318), LAPT5 (SEQ ID NO: 304 or 338), ARHGDIB (SEQ ID NO: 305 or 311), SLC43A3 (SEQ ID NO: 307), LCP1 (SEQ ID NO: 308), HCLS1 (SEQ ID NO: 309), CD53 (SEQ ID NO: 310), MZB1 (SEQ ID NO: 313), RASSF5 (SEQ ID NO: 314 or 386), FAM46C

(SEQ ID NO: 315), RCSD1 (SEQ ID NO: 316), IGJ (SEQ ID NO: 317), LPXN (SEQ ID NO: 319), ITGB7 (SEQ ID NO: 320), and/or GTSF1 (SEQ ID NO: 321). The expression level of the biomarker(s) may be determined using, e.g., a microarray, PCR, or other techniques described herein, for example, using a nucleic acid probe sequence based on the target sequences shown in Tables 1-4.

The biomarker BASP1 (SEQ ID NO: 215) may be used to assess a cancer patient's (e.g., a patient having cancer that is resistant to one or more cancer therapies other than irifolven) responsiveness to irifolven. The expression level of the biomarker BASP1 (SEQ ID NO: 215) may be assessed using nucleic acid amplification methods (e.g., PCR) or a device (e.g., a microarray). As is described above, the expression level of BASP1 (SEQ ID NO: 215) in the patient sample may then be compared, e.g., to the expression level of BASP1 (SEQ ID NO: 215) in a cell (e.g., a cancer cell) or tissue (e.g., a tumor tissue) known to be sensitive or resistant to treatment with irifolven and used to determine the cancer patient's responsiveness to irifolven. The biomarker BASP1 (SEQ ID NO: 215) may be used alone to predict cancer patient responsiveness to treatment with irifolven or in combination with one or more additional biomarkers (e.g., one, two, three, four, five, ten, or all of the biomarkers shown in Tables 1-4), such as ATP1B1 (SEQ ID NO: 201 or 219), UCHL1 (SEQ ID NO: 202), PTGR1 (SEQ ID NO: 203 or 210), NME7 (SEQ ID NO: 204), PLS3 (SEQ ID NO: 205), S100A10 (SEQ ID NO: 206), CD24 (SEQ ID NO: 207, 209, or 220), NQO1 (SEQ ID NO: 208 or 216), MYOF (SEQ ID NO: 211), LAPTM4B (SEQ ID NO: 212), CALD1 (SEQ ID NO: 213), PDGFC (SEQ ID NO: 214), ID1 (SEQ ID NO: 217), GJA1 (SEQ ID NO: 218), IGLC1 (SEQ ID NO: 301, 302, 303, or 318), LAPTM5 (SEQ ID NO: 304 or 338), ARHGDIB (SEQ ID NO: 305 or 311), SLC43A3 (SEQ ID NO: 307), LCP1 (SEQ ID NO: 308), HCLS1 (SEQ ID NO: 309), CD53 (SEQ ID NO: 310), MZB1 (SEQ ID NO: 313), RASSF5 (SEQ ID NO: 314 or 386), FAM46C (SEQ ID NO: 315), RCSD1 (SEQ ID NO: 316), IGJ (SEQ ID NO: 317), LPXN (SEQ ID NO: 319), ITGB7 (SEQ ID NO: 320), and/or GTSF1 (SEQ ID NO: 321). The expression level of the biomarker(s) may be determined using, e.g., a microarray, PCR, or other techniques described herein, for example, using a nucleic acid probe sequence based on the target sequences shown in Tables 1-4.

The biomarker ID1 (SEQ ID NO: 217) may be used to assess a cancer patient's (e.g., a patient having cancer that is resistant to one or more cancer therapies other than irifolven) responsiveness to irifolven. The expression level of the biomarker ID1 (SEQ ID NO: 217) may be assessed using nucleic acid amplification methods (e.g., PCR) or a device (e.g., a microarray). As is described above, the expression level of ID1 (SEQ ID NO: 217) in the patient sample may then be compared, e.g., to the expression level of ID1 (SEQ ID NO: 217) in a cell (e.g., a cancer cell) or tissue (e.g., a tumor tissue) known to be sensitive or resistant to treatment with irifolven and used to determine the cancer patient's responsiveness to irifolven. The biomarker ID1 (SEQ ID NO: 217) may be used alone to predict cancer patient responsiveness to treatment with irifolven or in combination with one or more additional biomarkers (e.g., one, two, three, four, five, ten, or all of the biomarkers shown in Tables 1-4), such as ATP1B1 (SEQ ID NO: 201 or 219), UCHL1 (SEQ ID NO: 202), PTGR1 (SEQ ID NO: 203 or 210), NME7 (SEQ ID NO: 204), PLS3 (SEQ ID NO: 205), S100A10 (SEQ ID NO: 206), CD24 (SEQ ID NO: 207, 209, or 220), NQO1 (SEQ ID NO: 208 or 216), MYOF (SEQ ID NO: 211), LAPTM4B (SEQ ID NO: 212), CALD1 (SEQ ID

NO: 213), PDGFC (SEQ ID NO: 214), BASP1 (SEQ ID NO: 215), GJA1 (SEQ ID NO: 218), IGLC1 (SEQ ID NO: 301, 302, 303, or 318), LAPTM5 (SEQ ID NO: 304 or 338), ARHGDIB (SEQ ID NO: 305 or 311), SLC43A3 (SEQ ID NO: 307), LCP1 (SEQ ID NO: 308), HCLS1 (SEQ ID NO: 309), CD53 (SEQ ID NO: 310), MZB1 (SEQ ID NO: 313), RASSF5 (SEQ ID NO: 314 or 386), FAM46C (SEQ ID NO: 315), RCSD1 (SEQ ID NO: 316), IGJ (SEQ ID NO: 317), LPXN (SEQ ID NO: 319), ITGB7 (SEQ ID NO: 320), and/or GTSF1 (SEQ ID NO: 321). The expression level of the biomarker(s) may be determined using, e.g., a microarray, PCR, or other techniques described herein, for example, using a nucleic acid probe sequence based on the target sequences shown in Tables 1-4.

The biomarker GJA1 (SEQ ID NO: 218) may be used to assess a cancer patient's (e.g., a patient having cancer that is resistant to one or more cancer therapies other than irifolven) responsiveness to irifolven. The expression level of the biomarker GJA1 (SEQ ID NO: 218) may be assessed using nucleic acid amplification methods (e.g., PCR) or a device (e.g., a microarray). As is described above, the expression level of GJA1 (SEQ ID NO: 218) in the patient sample may then be compared, e.g., to the expression level of GJA1 (SEQ ID NO: 218) in a cell (e.g., a cancer cell) or tissue (e.g., a tumor tissue) known to be sensitive or resistant to treatment with irifolven and used to determine the cancer patient's responsiveness to irifolven. The biomarker GJA1 (SEQ ID NO: 218) may be used alone to predict cancer patient responsiveness to treatment with irifolven or in combination with one or more additional biomarkers (e.g., one, two, three, four, five, ten, or all of the biomarkers shown in Tables 1-4), such as ATP1B1 (SEQ ID NO: 201 or 219), UCHL1 (SEQ ID NO: 202), PTGR1 (SEQ ID NO: 203 or 210), NME7 (SEQ ID NO: 204), PLS3 (SEQ ID NO: 205), S100A10 (SEQ ID NO: 206), CD24 (SEQ ID NO: 207, 209, or 220), NQO1 (SEQ ID NO: 208 or 216), MYOF (SEQ ID NO: 211), LAPTM4B (SEQ ID NO: 212), CALD1 (SEQ ID NO: 213), PDGFC (SEQ ID NO: 214), BASP1 (SEQ ID NO: 215), ID1 (SEQ ID NO: 217), IGLC1 (SEQ ID NO: 301, 302, 303, or 318), LAPTM5 (SEQ ID NO: 304 or 338), ARHGDIB (SEQ ID NO: 305 or 311), SLC43A3 (SEQ ID NO: 307), LCP1 (SEQ ID NO: 308), HCLS1 (SEQ ID NO: 309), CD53 (SEQ ID NO: 310), MZB1 (SEQ ID NO: 313), RASSF5 (SEQ ID NO: 314 or 386), FAM46C (SEQ ID NO: 315), RCSD1 (SEQ ID NO: 316), IGJ (SEQ ID NO: 317), LPXN (SEQ ID NO: 319), ITGB7 (SEQ ID NO: 320), and/or GTSF1 (SEQ ID NO: 321). The expression level of the biomarker(s) may be determined using, e.g., a microarray, PCR, or other techniques described herein, for example, using a nucleic acid probe sequence based on the target sequences shown in Tables 1-4.

The biomarker IGLC1 (SEQ ID NO: 301, 302, 303, or 318) may be used to assess a cancer patient's (e.g., a patient having cancer that is resistant to one or more cancer therapies other than irifolven) responsiveness to irifolven. The expression level of the biomarker IGLC1 (SEQ ID NO: 301, 302, 303, or 318) may be assessed using nucleic acid amplification methods (e.g., PCR) or a device (e.g., a microarray). As is described above, the expression level of IGLC1 (SEQ ID NO: 301, 302, 303, or 318) in the patient sample may then be compared, e.g., to the expression level of IGLC1 (SEQ ID NO: 301, 302, 303, or 318) in a cell (e.g., a cancer cell) or tissue (e.g., a tumor tissue) known to be sensitive or resistant to treatment with irifolven and used to determine the cancer patient's responsiveness to irifolven. The biomarker IGLC1 (SEQ ID NO: 301, 302, 303, or 318) may be used alone to predict cancer patient responsiveness

to treatment with irifolven or in combination with one or more additional biomarkers (e.g., one, two, three, four, five, ten, or all of the biomarkers shown in Tables 1-4), such as ATP1B1 (SEQ ID NO: 201 or 219), UCHL1 (SEQ ID NO: 202), PTGR1 (SEQ ID NO: 203 or 210), NME7 (SEQ ID NO: 204), PLS3 (SEQ ID NO: 205), S100A10 (SEQ ID NO: 206), CD24 (SEQ ID NO: 207, 209, or 220), NQO1 (SEQ ID NO: 208 or 216), MYOF (SEQ ID NO: 211), LAPTM4B (SEQ ID NO: 212), CALD1 (SEQ ID NO: 213), PDGFC (SEQ ID NO: 214), BASP1 (SEQ ID NO: 215), ID1 (SEQ ID NO: 217), GJA1 (SEQ ID NO: 218), LAPTM5 (SEQ ID NO: 304 or 338), ARHGDIB (SEQ ID NO: 305 or 311), SLC43A3 (SEQ ID NO: 307), LCP1 (SEQ ID NO: 308), HCLS1 (SEQ ID NO: 309), CD53 (SEQ ID NO: 310), MZB1 (SEQ ID NO: 313), RASSF5 (SEQ ID NO: 314 or 386), FAM46C (SEQ ID NO: 315), RCSD1 (SEQ ID NO: 316), IGJ (SEQ ID NO: 317), LPXN (SEQ ID NO: 319), ITGB7 (SEQ ID NO: 320), and/or GTSF1 (SEQ ID NO: 321). The expression level of the biomarker(s) may be determined using, e.g., a microarray, PCR, or other techniques described herein, for example, using a nucleic acid probe sequence based on the target sequences shown in Tables 1-4.

The biomarker LAPTM5 (SEQ ID NO: 304 or 338) may be used to assess a cancer patient's (e.g., a patient having cancer that is resistant to one or more cancer therapies other than irifolven) responsiveness to irifolven. The expression level of the biomarker LAPTM5 (SEQ ID NO: 304 or 338) may be assessed using nucleic acid amplification methods (e.g., PCR) or a device (e.g., a microarray). As is described above, the expression level of LAPTM5 (SEQ ID NO: 304 or 338) in the patient sample may then be compared, e.g., to the expression level of LAPTM5 (SEQ ID NO: 304 or 338) in a cell (e.g., a cancer cell) or tissue (e.g., a tumor tissue) known to be sensitive or resistant to treatment with irifolven and used to determine the cancer patient's responsiveness to irifolven. The biomarker LAPTM5 (SEQ ID NO: 304 or 338) may be used alone to predict cancer patient responsiveness to treatment with irifolven or in combination with one or more additional biomarkers (e.g., one, two, three, four, five, ten, or all of the biomarkers shown in Tables 1-4), such as ATP1B1 (SEQ ID NO: 201 or 219), UCHL1 (SEQ ID NO: 202), PTGR1 (SEQ ID NO: 203 or 210), NME7 (SEQ ID NO: 204), PLS3 (SEQ ID NO: 205), S100A10 (SEQ ID NO: 206), CD24 (SEQ ID NO: 207, 209, or 220), NQO1 (SEQ ID NO: 208 or 216), MYOF (SEQ ID NO: 211), LAPTM4B (SEQ ID NO: 212), CALD1 (SEQ ID NO: 213), PDGFC (SEQ ID NO: 214), BASP1 (SEQ ID NO: 215), ID1 (SEQ ID NO: 217), GJA1 (SEQ ID NO: 218), IGLC1 (SEQ ID NO: 301, 302, 303, or 318), ARHGDIB (SEQ ID NO: 305 or 311), SLC43A3 (SEQ ID NO: 307), LCP1 (SEQ ID NO: 308), HCLS1 (SEQ ID NO: 309), CD53 (SEQ ID NO: 310), MZB1 (SEQ ID NO: 313), RASSF5 (SEQ ID NO: 314 or 386), FAM46C (SEQ ID NO: 315), RCSD1 (SEQ ID NO: 316), IGJ (SEQ ID NO: 317), LPXN (SEQ ID NO: 319), ITGB7 (SEQ ID NO: 320), and/or GTSF1 (SEQ ID NO: 321). The expression level of the biomarker(s) may be determined using, e.g., a microarray, PCR, or other techniques described herein, for example, using a nucleic acid probe sequence based on the target sequences shown in Tables 1-4.

The biomarker ARHGDIB (SEQ ID NO: 305 or 311) may be used to assess a cancer patient's (e.g., a patient having cancer that is resistant to one or more cancer therapies other than irifolven) responsiveness to irifolven. The expression level of the biomarker ARHGDIB (SEQ ID NO: 305 or 311) may be assessed using nucleic acid amplification methods

(e.g., PCR) or a device (e.g., a microarray). As is described above, the expression level of ARHGDIB (SEQ ID NO: 305 or 311) in the patient sample may then be compared, e.g., to the expression level of ARHGDIB (SEQ ID NO: 305 or 311) in a cell (e.g., a cancer cell) or tissue (e.g., a tumor tissue) known to be sensitive or resistant to treatment with irifolven and used to determine the cancer patient's responsiveness to irifolven. The biomarker ARHGDIB (SEQ ID NO: 305 or 311) may be used alone to predict cancer patient responsiveness to treatment with irifolven or in combination with one or more additional biomarkers (e.g., one, two, three, four, five, ten, or all of the biomarkers shown in Tables 1-4), such as ATP1B1 (SEQ ID NO: 201 or 219), UCHL1 (SEQ ID NO: 202), PTGR1 (SEQ ID NO: 203 or 210), NME7 (SEQ ID NO: 204), PLS3 (SEQ ID NO: 205), S100A10 (SEQ ID NO: 206), CD24 (SEQ ID NO: 207, 209, or 220), NQO1 (SEQ ID NO: 208 or 216), MYOF (SEQ ID NO: 211), LAPTM4B (SEQ ID NO: 212), CALD1 (SEQ ID NO: 213), PDGFC (SEQ ID NO: 214), BASP1 (SEQ ID NO: 215), ID1 (SEQ ID NO: 217), GJA1 (SEQ ID NO: 218), IGLC1 (SEQ ID NO: 301, 302, 303, or 318), LAPTM5 (SEQ ID NO: 304 or 338), SLC43A3 (SEQ ID NO: 307), LCP1 (SEQ ID NO: 308), HCLS1 (SEQ ID NO: 309), CD53 (SEQ ID NO: 310), MZB1 (SEQ ID NO: 313), RASSF5 (SEQ ID NO: 314 or 386), FAM46C (SEQ ID NO: 315), RCSD1 (SEQ ID NO: 316), IGJ (SEQ ID NO: 317), LPXN (SEQ ID NO: 319), ITGB7 (SEQ ID NO: 320), and/or GTSF1 (SEQ ID NO: 321). The expression level of the biomarker(s) may be determined using, e.g., a microarray, PCR, or other techniques described herein, for example, using a nucleic acid probe sequence based on the target sequences shown in Tables 1-4.

The biomarker SLC43A3 (SEQ ID NO: 307) may be used to assess a cancer patient's (e.g., a patient having cancer that is resistant to one or more cancer therapies other than irifolven) responsiveness to irifolven. The expression level of the biomarker SLC43A3 (SEQ ID NO: 307) may be assessed using nucleic acid amplification methods (e.g., PCR) or a device (e.g., a microarray). As is described above, the expression level of SLC43A3 (SEQ ID NO: 307) in the patient sample may then be compared, e.g., to the expression level of SLC43A3 (SEQ ID NO: 307) in a cell (e.g., a cancer cell) or tissue (e.g., a tumor tissue) known to be sensitive or resistant to treatment with irifolven and used to determine the cancer patient's responsiveness to irifolven. The biomarker SLC43A3 (SEQ ID NO: 307) may be used alone to predict cancer patient responsiveness to treatment with irifolven or in combination with one or more additional biomarkers (e.g., one, two, three, four, five, ten, or all of the biomarkers shown in Tables 1-4), such as ATP1B1 (SEQ ID NO: 201 or 219), UCHL1 (SEQ ID NO: 202), PTGR1 (SEQ ID NO: 203 or 210), NME7 (SEQ ID NO: 204), PLS3 (SEQ ID NO: 205), S100A10 (SEQ ID NO: 206), CD24 (SEQ ID NO: 207, 209, or 220), NQO1 (SEQ ID NO: 208 or 216), MYOF (SEQ ID NO: 211), LAPTM4B (SEQ ID NO: 212), CALD1 (SEQ ID NO: 213), PDGFC (SEQ ID NO: 214), BASP1 (SEQ ID NO: 215), ID1 (SEQ ID NO: 217), GJA1 (SEQ ID NO: 218), IGLC1 (SEQ ID NO: 301, 302, 303, or 318), LAPTM5 (SEQ ID NO: 304 or 338), ARHGDIB (SEQ ID NO: 305 or 311), LCP1 (SEQ ID NO: 308), HCLS1 (SEQ ID NO: 309), CD53 (SEQ ID NO: 310), MZB1 (SEQ ID NO: 313), RASSF5 (SEQ ID NO: 314 or 386), FAM46C (SEQ ID NO: 315), RCSD1 (SEQ ID NO: 316), IGJ (SEQ ID NO: 317), LPXN (SEQ ID NO: 319), ITGB7 (SEQ ID NO: 320), and/or GTSF1 (SEQ ID NO: 321). The expression level of the biomarker(s) may be determined using, e.g., a microarray, PCR, or other techniques described herein, for

example, using a nucleic acid probe sequence based on the target sequences shown in Tables 1-4.

The biomarker LCP1 (SEQ ID NO: 308) may be used to assess a cancer patient's (e.g., a patient having cancer that is resistant to one or more cancer therapies other than irifolven) responsiveness to irifolven. The expression level of the biomarker LCP1 (SEQ ID NO: 308) may be assessed using nucleic acid amplification methods (e.g., PCR) or a device (e.g., a microarray). As is described above, the expression level of LCP1 (SEQ ID NO: 308) in the patient sample may then be compared, e.g., to the expression level of LCP1 (SEQ ID NO: 308) in a cell (e.g., a cancer cell) or tissue (e.g., a tumor tissue) known to be sensitive or resistant to treatment with irifolven and used to determine the cancer patient's responsiveness to irifolven. The biomarker LCP1 (SEQ ID NO: 308) may be used alone to predict cancer patient responsiveness to treatment with irifolven or in combination with one or more additional biomarkers (e.g., one, two, three, four, five, ten, or all of the biomarkers shown in Tables 1-4), such as ATP1B1 (SEQ ID NO: 201 or 219), UCHL1 (SEQ ID NO: 202), PTGR1 (SEQ ID NO: 203 or 210), NME7 (SEQ ID NO: 204), PLS3 (SEQ ID NO: 205), S100A10 (SEQ ID NO: 206), CD24 (SEQ ID NO: 207, 209, or 220), NQO1 (SEQ ID NO: 208 or 216), MYOF (SEQ ID NO: 211), LAPTM4B (SEQ ID NO: 212), CALD1 (SEQ ID NO: 213), PDGFC (SEQ ID NO: 214), BASP1 (SEQ ID NO: 215), ID1 (SEQ ID NO: 217), GJA1 (SEQ ID NO: 218), IGLC1 (SEQ ID NO: 301, 302, 303, or 318), LAPTM5 (SEQ ID NO: 304 or 338), ARHGDIB (SEQ ID NO: 305 or 311), SLC43A3 (SEQ ID NO: 307), HCLS1 (SEQ ID NO: 309), CD53 (SEQ ID NO: 310), MZB1 (SEQ ID NO: 313), RASSF5 (SEQ ID NO: 314 or 386), FAM46C (SEQ ID NO: 315), RCSD1 (SEQ ID NO: 316), IGJ (SEQ ID NO: 317), LPXN (SEQ ID NO: 319), ITGB7 (SEQ ID NO: 320), and/or GTSF1 (SEQ ID NO: 321). The expression level of the biomarker(s) may be determined using, e.g., a microarray, PCR, or other techniques described herein, for example, using a nucleic acid probe sequence based on the target sequences shown in Tables 1-4.

The biomarker HCLS1 (SEQ ID NO: 309) may be used to assess a cancer patient's (e.g., a patient having cancer that is resistant to one or more cancer therapies other than irifolven) responsiveness to irifolven. The expression level of the biomarker HCLS1 (SEQ ID NO: 309) may be assessed using nucleic acid amplification methods (e.g., PCR) or a device (e.g., a microarray). As is described above, the expression level of HCLS1 (SEQ ID NO: 309) in the patient sample may then be compared, e.g., to the expression level of HCLS1 (SEQ ID NO: 309) in a cell (e.g., a cancer cell) or tissue (e.g., a tumor tissue) known to be sensitive or resistant to treatment with irifolven and used to determine the cancer patient's responsiveness to irifolven. The biomarker HCLS1 (SEQ ID NO: 309) may be used alone to predict cancer patient responsiveness to treatment with irifolven or in combination with one or more additional biomarkers (e.g., one, two, three, four, five, ten, or all of the biomarkers shown in Tables 1-4), such as ATP1B1 (SEQ ID NO: 201 or 219), UCHL1 (SEQ ID NO: 202), PTGR1 (SEQ ID NO: 203 or 210), NME7 (SEQ ID NO: 204), PLS3 (SEQ ID NO: 205), S100A10 (SEQ ID NO: 206), CD24 (SEQ ID NO: 207, 209, or 220), NQO1 (SEQ ID NO: 208 or 216), MYOF (SEQ ID NO: 211), LAPTM4B (SEQ ID NO: 212), CALD1 (SEQ ID NO: 213), PDGFC (SEQ ID NO: 214), BASP1 (SEQ ID NO: 215), ID1 (SEQ ID NO: 217), GJA1 (SEQ ID NO: 218), IGLC1 (SEQ ID NO: 301, 302, 303, or 318), LAPTM5 (SEQ ID NO: 304 or 338), ARHGDIB (SEQ ID NO: 305 or 311), SLC43A3 (SEQ ID NO: 307), LCP1

(SEQ ID NO: 308), CD53 (SEQ ID NO: 310), MZB1 (SEQ ID NO: 313), RASSF5 (SEQ ID NO: 314 or 386), FAM46C (SEQ ID NO: 315), RCSD1 (SEQ ID NO: 316), IGJ (SEQ ID NO: 317), LPXN (SEQ ID NO: 319), ITGB7 (SEQ ID NO: 320), and/or GTSF1 (SEQ ID NO: 321). The expression level of the biomarker(s) may be determined using, e.g., a microarray, PCR, or other techniques described herein, for example, using a nucleic acid probe sequence based on the target sequences shown in Tables 1-4.

The biomarker CD53 (SEQ ID NO: 310) may be used to assess a cancer patient's (e.g., a patient having cancer that is resistant to one or more cancer therapies other than irifolven) responsiveness to irifolven. The expression level of the biomarker CD53 (SEQ ID NO: 310) may be assessed using nucleic acid amplification methods (e.g., PCR) or a device (e.g., a microarray). As is described above, the expression level of CD53 (SEQ ID NO: 310) in the patient sample may then be compared, e.g., to the expression level of CD53 (SEQ ID NO: 310) in a cell (e.g., a cancer cell) or tissue (e.g., a tumor tissue) known to be sensitive or resistant to treatment with irifolven and used to determine the cancer patient's responsiveness to irifolven. The biomarker CD53 (SEQ ID NO: 310) may be used alone to predict cancer patient responsiveness to treatment with irifolven or in combination with one or more additional biomarkers (e.g., one, two, three, four, five, ten, or all of the biomarkers shown in Tables 1-4), such as ATP1B1 (SEQ ID NO: 201 or 219), UCHL1 (SEQ ID NO: 202), PTGR1 (SEQ ID NO: 203 or 210), NME7 (SEQ ID NO: 204), PLS3 (SEQ ID NO: 205), S100A10 (SEQ ID NO: 206), CD24 (SEQ ID NO: 207, 209, or 220), NQO1 (SEQ ID NO: 208 or 216), MYOF (SEQ ID NO: 211), LAPTM4B (SEQ ID NO: 212), CALD1 (SEQ ID NO: 213), PDGFC (SEQ ID NO: 214), BASP1 (SEQ ID NO: 215), ID1 (SEQ ID NO: 217), GJA1 (SEQ ID NO: 218), IGLC1 (SEQ ID NO: 301, 302, 303, or 318), LAPTM5 (SEQ ID NO: 304 or 338), ARHGDIB (SEQ ID NO: 305 or 311), SLC43A3 (SEQ ID NO: 307), LCP1 (SEQ ID NO: 308), HCLS1 (SEQ ID NO: 309), MZB1 (SEQ ID NO: 313), RASSF5 (SEQ ID NO: 314 or 386), FAM46C (SEQ ID NO: 315), RCSD1 (SEQ ID NO: 316), IGJ (SEQ ID NO: 317), LPXN (SEQ ID NO: 319), ITGB7 (SEQ ID NO: 320), and/or GTSF1 (SEQ ID NO: 321). The expression level of the biomarker(s) may be determined using, e.g., a microarray, PCR, or other techniques described herein, for example, using a nucleic acid probe sequence based on the target sequences shown in Tables 1-4.

The biomarker MZB1 (SEQ ID NO: 313) may be used to assess a cancer patient's (e.g., a patient having cancer that is resistant to one or more cancer therapies other than irifolven) responsiveness to irifolven. The expression level of the biomarker MZB1 (SEQ ID NO: 313) may be assessed using nucleic acid amplification methods (e.g., PCR) or a device (e.g., a microarray). As is described above, the expression level of MZB1 (SEQ ID NO: 313) in the patient sample may then be compared, e.g., to the expression level of MZB1 (SEQ ID NO: 313) in a cell (e.g., a cancer cell) or tissue (e.g., a tumor tissue) known to be sensitive or resistant to treatment with irifolven and used to determine the cancer patient's responsiveness to irifolven. The biomarker MZB1 (SEQ ID NO: 313) may be used alone to predict cancer patient responsiveness to treatment with irifolven or in combination with one or more additional biomarkers (e.g., one, two, three, four, five, ten, or all of the biomarkers shown in Tables 1-4), such as ATP1B1 (SEQ ID NO: 201 or 219), UCHL1 (SEQ ID NO: 202), PTGR1 (SEQ ID NO: 203 or 210), NME7 (SEQ ID NO: 204), PLS3 (SEQ ID NO: 205), S100A10 (SEQ ID NO: 206), CD24 (SEQ ID NO: 207, 209,

or 220), NQO1 (SEQ ID NO: 208 or 216), MYOF (SEQ ID NO: 211), LAPTM4B (SEQ ID NO: 212), CALD1 (SEQ ID NO: 213), PDGFC (SEQ ID NO: 214), BASP1 (SEQ ID NO: 215), ID1 (SEQ ID NO: 217), GJA1 (SEQ ID NO: 218), IGLC1 (SEQ ID NO: 301, 302, 303, or 318), LAPTM5 (SEQ ID NO: 304 or 338), ARHGDIB (SEQ ID NO: 305 or 311), SLC43A3 (SEQ ID NO: 307), LCP1 (SEQ ID NO: 308), HCLS1 (SEQ ID NO: 309), CD53 (SEQ ID NO: 310), RASSF5 (SEQ ID NO: 314 or 386), FAM46C (SEQ ID NO: 315), RCSD1 (SEQ ID NO: 316), IGJ (SEQ ID NO: 317), LPXN (SEQ ID NO: 319), ITGB7 (SEQ ID NO: 320), and/or GTSF1 (SEQ ID NO: 321). The expression level of the biomarker(s) may be determined using, e.g., a microarray, PCR, or other techniques described herein, for example, using a nucleic acid probe sequence based on the target sequences shown in Tables 1-4.

The biomarker RASSF5 (SEQ ID NO: 314 or 386) may be used to assess a cancer patient's (e.g., a patient having cancer that is resistant to one or more cancer therapies other than irifolven) responsiveness to irifolven. The expression level of the biomarker RASSF5 (SEQ ID NO: 314 or 386) may be assessed using nucleic acid amplification methods (e.g., PCR) or a device (e.g., a microarray). As is described above, the expression level of RASSF5 (SEQ ID NO: 314 or 386) in the patient sample may then be compared, e.g., to the expression level of RASSF5 (SEQ ID NO: 314 or 386) in a cell (e.g., a cancer cell) or tissue (e.g., a tumor tissue) known to be sensitive or resistant to treatment with irifolven and used to determine the cancer patient's responsiveness to irifolven. The biomarker RASSF5 (SEQ ID NO: 314 or 386) may be used alone to predict cancer patient responsiveness to treatment with irifolven or in combination with one or more additional biomarkers (e.g., one, two, three, four, five, ten, or all of the biomarkers shown in Tables 1-4), such as ATP1B1 (SEQ ID NO: 201 or 219), UCHL1 (SEQ ID NO: 202), PTGR1 (SEQ ID NO: 203 or 210), NME7 (SEQ ID NO: 204), PLS3 (SEQ ID NO: 205), S100A10 (SEQ ID NO: 206), CD24 (SEQ ID NO: 207, 209, or 220), NQO1 (SEQ ID NO: 208 or 216), MYOF (SEQ ID NO: 211), LAPTM4B (SEQ ID NO: 212), CALD1 (SEQ ID NO: 213), PDGFC (SEQ ID NO: 214), BASP1 (SEQ ID NO: 215), ID1 (SEQ ID NO: 217), GJA1 (SEQ ID NO: 218), IGLC1 (SEQ ID NO: 301, 302, 303, or 318), LAPTM5 (SEQ ID NO: 304 or 338), ARHGDIB (SEQ ID NO: 305 or 311), SLC43A3 (SEQ ID NO: 307), LCP1 (SEQ ID NO: 308), HCLS1 (SEQ ID NO: 309), CD53 (SEQ ID NO: 310), MZB1 (SEQ ID NO: 313), FAM46C (SEQ ID NO: 315), RCSD1 (SEQ ID NO: 316), IGJ (SEQ ID NO: 317), LPXN (SEQ ID NO: 319), ITGB7 (SEQ ID NO: 320), and/or GTSF1 (SEQ ID NO: 321). The expression level of the biomarker(s) may be determined using, e.g., a microarray, PCR, or other techniques described herein, for example, using a nucleic acid probe sequence based on the target sequences shown in Tables 1-4.

The biomarker FAM46C (SEQ ID NO: 315) may be used to assess a cancer patient's (e.g., a patient having cancer that is resistant to one or more cancer therapies other than irifolven) responsiveness to irifolven. The expression level of the biomarker FAM46C (SEQ ID NO: 315) may be assessed using nucleic acid amplification methods (e.g., PCR) or a device (e.g., a microarray). As is described above, the expression level of FAM46C (SEQ ID NO: 315) in the patient sample may then be compared, e.g., to the expression level of FAM46C (SEQ ID NO: 315) in a cell (e.g., a cancer cell) or tissue (e.g., a tumor tissue) known to be sensitive or resistant to treatment with irifolven and used to determine the cancer patient's responsiveness to irifolven. The bio-

marker FAM46C (SEQ ID NO: 315) may be used alone to predict cancer patient responsiveness to treatment with irifolven or in combination with one or more additional biomarkers (e.g., one, two, three, four, five, ten, or all of the biomarkers shown in Tables 1-4), such as ATP1B1 (SEQ ID NO: 201 or 219), UCHL1 (SEQ ID NO: 202), PTGR1 (SEQ ID NO: 203 or 210), NME7 (SEQ ID NO: 204), PLS3 (SEQ ID NO: 205), S100A10 (SEQ ID NO: 206), CD24 (SEQ ID NO: 207, 209, or 220), NQO1 (SEQ ID NO: 208 or 216), MYOF (SEQ ID NO: 211), LAPTM4B (SEQ ID NO: 212), CALD1 (SEQ ID NO: 213), PDGFC (SEQ ID NO: 214), BASP1 (SEQ ID NO: 215), ID1 (SEQ ID NO: 217), GJA1 (SEQ ID NO: 218), IGLC1 (SEQ ID NO: 301, 302, 303, or 318), LAPTM5 (SEQ ID NO: 304 or 338), ARHGDIB (SEQ ID NO: 305 or 311), SLC43A3 (SEQ ID NO: 307), LCP1 (SEQ ID NO: 308), HCLS1 (SEQ ID NO: 309), CD53 (SEQ ID NO: 310), MZB1 (SEQ ID NO: 313), RASSF5 (SEQ ID NO: 314 or 386), FRCSD1 (SEQ ID NO: 316), IGJ (SEQ ID NO: 317), LPXN (SEQ ID NO: 319), ITGB7 (SEQ ID NO: 320), and/or GTSF1 (SEQ ID NO: 321). The expression level of the biomarker(s) may be determined using, e.g., a microarray, PCR, or other techniques described herein, for example, using a nucleic acid probe sequence based on the target sequences shown in Tables 1-4.

The biomarker RCSD1 (SEQ ID NO: 316) may be used to assess a cancer patient's (e.g., a patient having cancer that is resistant to one or more cancer therapies other than irifolven) responsiveness to irifolven. The expression level of the biomarker RCSD1 (SEQ ID NO: 316) may be assessed using nucleic acid amplification methods (e.g., PCR) or a device (e.g., a microarray). As is described above, the expression level of RCSD1 (SEQ ID NO: 316) in the patient sample may then be compared, e.g., to the expression level of RCSD1 (SEQ ID NO: 316) in a cell (e.g., a cancer cell) or tissue (e.g., a tumor tissue) known to be sensitive or resistant to treatment with irifolven and used to determine the cancer patient's responsiveness to irifolven. The biomarker RCSD1 (SEQ ID NO: 316) may be used alone to predict cancer patient responsiveness to treatment with irifolven or in combination with one or more additional biomarkers (e.g., one, two, three, four, five, ten, or all of the biomarkers shown in Tables 1-4), such as ATP1B1 (SEQ ID NO: 201 or 219), UCHL1 (SEQ ID NO: 202), PTGR1 (SEQ ID NO: 203 or 210), NME7 (SEQ ID NO: 204), PLS3 (SEQ ID NO: 205), S100A10 (SEQ ID NO: 206), CD24 (SEQ ID NO: 207, 209, or 220), NQO1 (SEQ ID NO: 208 or 216), MYOF (SEQ ID NO: 211), LAPTM4B (SEQ ID NO: 212), CALD1 (SEQ ID NO: 213), PDGFC (SEQ ID NO: 214), BASP1 (SEQ ID NO: 215), ID1 (SEQ ID NO: 217), GJA1 (SEQ ID NO: 218), IGLC1 (SEQ ID NO: 301, 302, 303, or 318), LAPTM5 (SEQ ID NO: 304 or 338), ARHGDIB (SEQ ID NO: 305 or 311), SLC43A3 (SEQ ID NO: 307), LCP1 (SEQ ID NO: 308), HCLS1 (SEQ ID NO: 309), CD53 (SEQ ID NO: 310), MZB1 (SEQ ID NO: 313), RASSF5 (SEQ ID NO: 314 or 386), FAM46C (SEQ ID NO: 315), IGJ (SEQ ID NO: 317), LPXN (SEQ ID NO: 319), ITGB7 (SEQ ID NO: 320), and/or GTSF1 (SEQ ID NO: 321). The expression level of the biomarker(s) may be determined using, e.g., a microarray, PCR, or other techniques described herein, for example, using a nucleic acid probe sequence based on the target sequences shown in Tables 1-4.

The biomarker IGJ (SEQ ID NO: 317) may be used to assess a cancer patient's (e.g., a patient having cancer that is resistant to one or more cancer therapies other than irifolven) responsiveness to irifolven. The expression level of the biomarker IGJ (SEQ ID NO: 317) may be assessed using nucleic acid amplification methods (e.g., PCR) or a device

(e.g., a microarray). As is described above, the expression level of IGJ (SEQ ID NO: 317) in the patient sample may then be compared, e.g., to the expression level of IGJ (SEQ ID NO: 317) in a cell (e.g., a cancer cell) or tissue (e.g., a tumor tissue) known to be sensitive or resistant to treatment with irifolven and used to determine the cancer patient's responsiveness to irifolven. The biomarker IGJ (SEQ ID NO: 317) may be used alone to predict cancer patient responsiveness to treatment with irifolven or in combination with one or more additional biomarkers (e.g., one, two, three, four, five, ten, or all of the biomarkers shown in Tables 1-4), such as ATP1B1 (SEQ ID NO: 201 or 219), UCHL1 (SEQ ID NO: 202), PTGR1 (SEQ ID NO: 203 or 210), NME7 (SEQ ID NO: 204), PLS3 (SEQ ID NO: 205), S100A10 (SEQ ID NO: 206), CD24 (SEQ ID NO: 207, 209, or 220), NQO1 (SEQ ID NO: 208 or 216), MYOF (SEQ ID NO: 211), LAPTM4B (SEQ ID NO: 212), CALD1 (SEQ ID NO: 213), PDGFC (SEQ ID NO: 214), BASP1 (SEQ ID NO: 215), ID1 (SEQ ID NO: 217), GJA1 (SEQ ID NO: 218), IGLC1 (SEQ ID NO: 301, 302, 303, or 318), LAPTM5 (SEQ ID NO: 304 or 338), ARHGDIB (SEQ ID NO: 305 or 311), SLC43A3 (SEQ ID NO: 307), LCP1 (SEQ ID NO: 308), HCLS1 (SEQ ID NO: 309), CD53 (SEQ ID NO: 310), MZB1 (SEQ ID NO: 313), RASSF5 (SEQ ID NO: 314 or 386), FAM46C (SEQ ID NO: 315), RCSD1 (SEQ ID NO: 316), LPXN (SEQ ID NO: 319), ITGB7 (SEQ ID NO: 320), and/or GTSF1 (SEQ ID NO: 321). The expression level of the biomarker(s) may be determined using, e.g., a microarray, PCR, or other techniques described herein, for example, using a nucleic acid probe sequence based on the target sequences shown in Tables 1-4.

The biomarker LPXN (SEQ ID NO: 319) may be used to assess a cancer patient's (e.g., a patient having cancer that is resistant to one or more cancer therapies other than irifolven) responsiveness to irifolven. The expression level of the biomarker LPXN (SEQ ID NO: 319) may be assessed using nucleic acid amplification methods (e.g., PCR) or a device (e.g., a microarray). As is described above, the expression level of LPXN (SEQ ID NO: 319) in the patient sample may then be compared, e.g., to the expression level of LPXN (SEQ ID NO: 319) in a cell (e.g., a cancer cell) or tissue (e.g., a tumor tissue) known to be sensitive or resistant to treatment with irifolven and used to determine the cancer patient's responsiveness to irifolven. The biomarker LPXN (SEQ ID NO: 319) may be used alone to predict cancer patient responsiveness to treatment with irifolven or in combination with one or more additional biomarkers (e.g., one, two, three, four, five, ten, or all of the biomarkers shown in Tables 1-4), such as ATP1B1 (SEQ ID NO: 201 or 219), UCHL1 (SEQ ID NO: 202), PTGR1 (SEQ ID NO: 203 or 210), NME7 (SEQ ID NO: 204), PLS3 (SEQ ID NO: 205), S100A10 (SEQ ID NO: 206), CD24 (SEQ ID NO: 207, 209, or 220), NQO1 (SEQ ID NO: 208 or 216), MYOF (SEQ ID NO: 211), LAPTM4B (SEQ ID NO: 212), CALD1 (SEQ ID NO: 213), PDGFC (SEQ ID NO: 214), BASP1 (SEQ ID NO: 215), ID1 (SEQ ID NO: 217), GJA1 (SEQ ID NO: 218), IGLC1 (SEQ ID NO: 301, 302, 303, or 318), LAPTM5 (SEQ ID NO: 304 or 338), ARHGDIB (SEQ ID NO: 305 or 311), SLC43A3 (SEQ ID NO: 307), LCP1 (SEQ ID NO: 308), HCLS1 (SEQ ID NO: 309), CD53 (SEQ ID NO: 310), MZB1 (SEQ ID NO: 313), RASSF5 (SEQ ID NO: 314 or 386), FAM46C (SEQ ID NO: 315), RCSD1 (SEQ ID NO: 316), IGJ (SEQ ID NO: 317), ITGB7 (SEQ ID NO: 320), and/or GTSF1 (SEQ ID NO: 321). The expression level of the biomarker(s) may be determined using, e.g., a microarray, PCR, or other techniques described herein, for example,

using a nucleic acid probe sequence based on the target sequences shown in Tables 1-4.

The biomarker ITGB7 (SEQ ID NO: 320) may be used to assess a cancer patient's (e.g., a patient having cancer that is resistant to one or more cancer therapies other than irifolven) responsiveness to irifolven. The expression level of the biomarker ITGB7 (SEQ ID NO: 320) may be assessed using nucleic acid amplification methods (e.g., PCR) or a device (e.g., a microarray). As is described above, the expression level of ITGB7 (SEQ ID NO: 320) in the patient sample may then be compared, e.g., to the expression level of ITGB7 (SEQ ID NO: 320) in a cell (e.g., a cancer cell) or tissue (e.g., a tumor tissue) known to be sensitive or resistant to treatment with irifolven and used to determine the cancer patient's responsiveness to irifolven. The biomarker ITGB7 (SEQ ID NO: 320) may be used alone to predict cancer patient responsiveness to treatment with irifolven or in combination with one or more additional biomarkers (e.g., one, two, three, four, five, ten, or all of the biomarkers shown in Tables 1-4), such as ATP1B1 (SEQ ID NO: 201 or 219), UCHL1 (SEQ ID NO: 202), PTGR1 (SEQ ID NO: 203 or 210), NME7 (SEQ ID NO: 204), PLS3 (SEQ ID NO: 205), S100A10 (SEQ ID NO: 206), CD24 (SEQ ID NO: 207, 209, or 220), NQO1 (SEQ ID NO: 208 or 216), MYOF (SEQ ID NO: 211), LAPTM4B (SEQ ID NO: 212), CALD1 (SEQ ID NO: 213), PDGFC (SEQ ID NO: 214), BASP1 (SEQ ID NO: 215), ID1 (SEQ ID NO: 217), GJA1 (SEQ ID NO: 218), IGLC1 (SEQ ID NO: 301, 302, 303, or 318), LAPTM5 (SEQ ID NO: 304 or 338), ARHGDIB (SEQ ID NO: 305 or 311), SLC43A3 (SEQ ID NO: 307), LCP1 (SEQ ID NO: 308), HCLS1 (SEQ ID NO: 309), CD53 (SEQ ID NO: 310), MZB1 (SEQ ID NO: 313), RASSF5 (SEQ ID NO: 314 or 386), FAM46C (SEQ ID NO: 315), RCSD1 (SEQ ID NO: 316), IGJ (SEQ ID NO: 317), LPXN (SEQ ID NO: 319), and/or GTSF1 (SEQ ID NO: 321). The expression level of the biomarker(s) may be determined using, e.g., a microarray, PCR, or other techniques described herein, for example, using a nucleic acid probe sequence based on the target sequences shown in Tables 1-4.

The biomarker GTSF1 (SEQ ID NO: 321) may be used to assess a cancer patient's (e.g., a patient having cancer that is resistant to one or more cancer therapies other than irifolven) responsiveness to irifolven. The expression level of the biomarker GTSF1 (SEQ ID NO: 321) may be assessed using nucleic acid amplification methods (e.g., PCR) or a device (e.g., a microarray). As is described above, the expression level of GTSF1 (SEQ ID NO: 321) in the patient sample may then be compared, e.g., to the expression level of GTSF1 (SEQ ID NO: 321) in a cell (e.g., a cancer cell) or tissue (e.g., a tumor tissue) known to be sensitive or resistant to treatment with irifolven and used to determine the cancer patient's responsiveness to irifolven. The biomarker GTSF1 (SEQ ID NO: 321) may be used alone to predict cancer patient responsiveness to treatment with irifolven or in combination with one or more additional biomarkers (e.g., one, two, three, four, five, ten, or all of the biomarkers shown in Tables 1-4), such as ATP1B1 (SEQ ID NO: 201 or 219), UCHL1 (SEQ ID NO: 202), PTGR1 (SEQ ID NO: 203 or 210), NME7 (SEQ ID NO: 204), PLS3 (SEQ ID NO: 205), S100A10 (SEQ ID NO: 206), CD24 (SEQ ID NO: 207, 209, or 220), NQO1 (SEQ ID NO: 208 or 216), MYOF (SEQ ID NO: 211), LAPTM4B (SEQ ID NO: 212), CALD1 (SEQ ID NO: 213), PDGFC (SEQ ID NO: 214), BASP1 (SEQ ID NO: 215), ID1 (SEQ ID NO: 217), GJA1 (SEQ ID NO: 218), IGLC1 (SEQ ID NO: 301, 302, 303, or 318), LAPTM5 (SEQ ID NO: 304 or 338), ARHGDIB (SEQ ID NO: 305 or 311), SLC43A3 (SEQ ID NO: 307), LCP1 (SEQ ID NO:

308), HCLS1 (SEQ ID NO: 309), CD53 (SEQ ID NO: 310), MZB1 (SEQ ID NO: 313), RASSF5 (SEQ ID NO: 314 or 386), FAM46C (SEQ ID NO: 315), RCSD1 (SEQ ID NO: 316), IGJ (SEQ ID NO: 317), LPXN (SEQ ID NO: 319), and/or ITGB7 (SEQ ID NO: 320). The expression level of the biomarker(s) may be determined using, e.g., a microarray, PCR, or other techniques described herein, for example, using a nucleic acid probe sequence based on the target sequences shown in Tables 1-4.

Methods of Treatment

The diagnostic methods of the invention permit the assessment of whether a patient is likely to be responsive to treatment with irifolven, and can thus be used to direct the patient's treatment (e.g., as a first line therapy and/or as a second or third line therapy). A patient to be treated or tested for responsiveness to irifolven according to the methods may include, e.g., a patient that has been diagnosed with cancer, a patient that has not received a cancer treatment (e.g., irifolven, an anti-cancer agent other than irifolven, or radiation), a patient that has received a cancer treatment (e.g., an anti-cancer agent other than irifolven or radiation), or a patient during treatment with irifolven.

For example, the patient may have a solid tumor or a hematological cancer, such as a cancer type selected from prostate cancer, ovarian cancer (e.g., ovarian adenocarcinoma or embryonal carcinoma), liver cancer (e.g., hepatocellular carcinoma (HCC) or hepatoma), myeloma (e.g., multiple myeloma), colorectal cancer (e.g., colon cancer and rectal cancer), leukemia (e.g., acute myeloid leukemia, acute lymphoid leukemia, chronic myeloid leukemia, chronic lymphocytic leukemia, acute myeloblastic leukemia, acute promyelocytic leukemia, acute myelomonocytic leukemia, acute monocytic leukemia, acute erythroleukemia, and chronic leukemia), myelodysplastic syndrome, lymphoma (e.g., diffuse large B-cell lymphoma, cutaneous T-cell lymphoma, peripheral T-cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, Waldenstrom's macroglobulinemia, and lymphocytic lymphoma), cervical cancer, esophageal cancer, melanoma, glioma (e.g., oligodendroglioma), pancreatic cancer (e.g., adenosquamous carcinoma, signet ring cell carcinoma, hepatoid carcinoma, colloid carcinoma, islet cell carcinoma, and pancreatic neuroendocrine carcinoma), gastrointestinal stromal tumor, sarcoma (e.g., fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, leiomyosarcoma, Ewing's sarcoma, and rhabdomyosarcoma), breast cancer (e.g., medullary carcinoma), ER-positive cancer, bladder cancer, head and neck cancer (e.g., squamous cell carcinoma of the head and neck), lung cancer (e.g., non-small cell lung carcinoma, large cell carcinoma, bronchogenic carcinoma, and papillary adenocarcinoma), metastatic cancer, oral cavity cancer, uterine cancer, testicular cancer (e.g., seminoma and embryonal carcinoma), skin cancer (e.g., squamous cell carcinoma and basal cell carcinoma), thyroid cancer (e.g., papillary carcinoma and medullary carcinoma), brain cancer (e.g., astrocytoma and craniopharyngioma), stomach cancer, intra-epithelial cancer, bone cancer, biliary tract cancer, eye cancer, larynx cancer, kidney cancer (e.g., renal cell carcinoma and Wilms tumor), gastric cancer, blastoma (e.g., nephroblastoma, medulloblastoma, hemangioblastoma, neuroblastoma, and retinoblastoma), polycythemia vera, chordoma, synovioma, mesothelioma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, cystadenocarcinoma, bile duct carcinoma, choriocarcinoma, epithelial carcinoma, ependymoma, pinealoma, acoustic neuroma, schwannoma, meningioma, pitu-

itary adenoma, nerve sheath tumor, cancer of the small intestine, cancer of the endocrine system, cancer of the penis, cancer of the urethra, cutaneous or intraocular melanoma, a gynecologic tumor, solid tumors of childhood, and neoplasms of the central nervous system. In particular, the cancer of the patient is, e.g., prostate cancer, ovarian cancer, hepatocellular carcinoma (HCC), multiple myeloma, breast cancer, acute myelogenous leukemia (AML), acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), myelodysplastic syndrome (MDS), chronic myelogenous leukemia-chronic phase (CMLCP), diffuse large B-cell lymphoma (DLBCL), cutaneous T-cell lymphoma (CTCL), peripheral T-cell lymphoma (PTCL), Hodgkin's lymphoma, cervical cancer, renal cell carcinoma (RCC), esophageal cancer, melanoma, glioma, pancreatic cancer, gastrointestinal stromal tumors (GIST), sarcoma, estrogen receptor-positive (ERpos) breast cancer, non-small cell lung carcinoma (NSCLC), colon cancer, bladder cancer, or squamous cell carcinoma of the head and neck (SCCHN).

The patient may have a cancer (e.g., prostate cancer, ovarian cancer, or hepatocellular carcinoma (HCC)) that is resistant to one or more cancer therapies other than irifolven (e.g., docetaxel, cabazitaxel, mitoxantrone, estramustine, prednisone, carboplatin, bevacizumab, paclitaxel, gemcitabine, doxorubicin, topotecan, etoposide, tamoxifen, letrozole, sorafenib, fluorouracil, capecitabine, oxaliplatin, interferon-alpha, 5-fluorouracil (5-FU), a histone deacetylase (HDAC) inhibitor, ipilimumab, bortezomib, carfilzomib, thalidomide, lenalidomide, pomalidomide, dexamethasone, cyclophosphamide, vincristine, melphalan, tegafur, irinotecan, cetuximab, leucovorin, SN-38, everolimus, temsirolimus, bleomycin, lomustine, depsipeptide, erlotinib, cisplatin, busulfan, epirubicin, arsenic trioxide, bendamustine, fulvestrant, teniposide, adriamycin, decitabine, estramustine, azaguanine, aclarubicin, mitomycin, paclitaxel, taxotere, APO010, ara-c, methylprednisolone, methotrexate, methyl-gag, belinostat, idarubicin, IL4-PR38, valproic acid, all-trans retinoic acid (ATRA), cytoxan, suberoylanilide hydroxamic acid, leukeran, fludarabine, vinblastine, dacarbazine, hydroxyurea, tegafur, daunorubicin, mechlorethamine, streptozocin, carmustine, mercaptopurine, dactinomycin, tretinoin, ifosfamide, floxuridine, thioguanine, PSC 833, herceptin, celecoxib, iressa, anastrozole, and rituximab), surgery, or radiation. The patient may also have experienced a recurrence following a treatment with a cancer therapy other than irifolven, surgery, or radiation.

A patient found to be responsive to irifolven according to the methods of the invention may be preferentially selected for treatment with irifolven. For example, a patient can be identified as responsive to irifolven by determining the expression level of one or more biomarkers (e.g., one or more of the biomarkers shown in Tables 1-4, such as ATP1B1 (SEQ ID NO: 201)) in a biological sample (e.g., a tumor sample) obtained from the patient, and subsequently administered irifolven. Alternatively, a patient can be identified as less likely to be responsive to irifolven by determining the expression level of one or more biomarkers (e.g., one or more of the biomarkers shown in Tables 1-4, such as ATP1B1 (SEQ ID NO: 201)) in a biological sample obtained from the patient. If the patient exhibits expression levels of one or more biomarkers indicative of non-responsiveness to irifolven, the patient may be treated with or offered a treatment with an agent other than irifolven. In particular, the patient may be treated with, e.g., radiation and/or administration of a therapeutic agent, such as docetaxel, cabazitaxel, mitoxantrone, estramustine, prednisone, carboplatin, bevacizumab, paclitaxel, gemcitabine, doxorubicin, topote-

can, etoposide, tamoxifen, letrozole, sorafenib, fluorouracil, capecitabine, oxaliplatin, interferon-alpha, 5-fluorouracil (5-FU), a histone deacetylase (HDAC) inhibitor, ipilimumab, bortezomib, carfilzomib, thalidomide, lenalidomide, pomalidomide, dexamethasone, cyclophosphamide, vincristine, melphalan, tegafur, irinotecan, cetuximab, leucovorin, SN-38, everolimus, temsirolimus, bleomycin, lomustine, depsiptide, erlotinib, cisplatin, busulfan, epirubicin, arsenic trioxide, bendamustine, fulvestrant, teniposide, adriamycin, decitabine, estramustine, azaguanine, aclarubicin, mitomycin, paclitaxel, taxotere, APO010, ara-c, methylprednisolone, methotrexate, methyl-gag, belinostat, idarubicin, IL4-PR38, valproic acid, all-trans retinoic acid (ATRA), cytoxan, suberoylanilide hydroxamic acid, leukeran, fludarabine, vinblastine, dacarbazine, hydroxyurea, tegafur, daunorubicin, mechlorethamine, streptozocin, carmustine, mercaptopurine, dactinomycin, tretinoin, ifosfamide, floxuridine, thioguanine, PSC 833, herceptin, celecoxib, iressa, anastrozole, or rituximab.

Administration of Irofulven

Once a patient has been determined to be responsive to irofulven, according to the methods described herein, irofulven may be administered to the patient, for example, parenterally, enterally, or topically. Enteral routes of irofulven administration include oral, buccal, sublabial, sublingual, or by inhalation. Parenteral routes of irofulven administration include intravenous, transdermal, intradermal, intramuscular, intra-arterial, intracranial, subcutaneous, intraorbital, intraventricular, intraspinal, intraperitoneal, or intranasal. The preferred route for administration of irofulven may be intravenous, such as intravenous infusion.

Irofulven can be administered at, e.g., a dose of about 0.05 mg/kg to 5 mg/kg, about 0.06 mg/kg to 4 mg/kg, about 0.1 mg/kg to 3 mg/kg, about 0.2 mg/kg to 2 mg/kg, about 0.3 mg/kg to 1 mg/kg, about 0.4 mg/kg to 1 mg/kg, about 0.2 mg/kg to 4 mg/kg, about 0.35 mg/kg to 4.5 mg/kg, about 0.25 mg/kg to 3.5 mg/kg, about 0.15 mg/kg to 2.5 mg/kg, about 0.45 mg/kg to about 1 mg/kg, about 0.45 mg/kg to about 2 mg/kg, or about 0.45 mg/kg to about 4 mg/kg. Irofulven may be administered at a frequency of, e.g., at least once hourly, once daily, twice daily, once weekly, once every two weeks, once every three weeks, once every four weeks, once monthly, once every two months, once every three months, once every six months, or once every year.

For example, irofulven may be administered at a treatment regimen of, e.g., about 0.05 mg/kg to 5 mg/kg, about 0.06 mg/kg to 4 mg/kg, about 0.1 mg/kg to 3 mg/kg, about 0.2 mg/kg to 2 mg/kg, about 0.3 mg/kg to 1 mg/kg, about 0.4 mg/kg to 1 mg/kg, about 0.2 mg/kg to 4 mg/kg, about 0.35 mg/kg to 4.5 mg/kg, about 0.25 mg/kg to 3.5 mg/kg, about 0.15 mg/kg to 2.5 mg/kg, about 0.45 mg/kg to about 1 mg/kg, about 0.45 mg/kg to about 2 mg/kg, or about 0.45 mg/kg to about 4 mg/kg on day 1 and day 8 every 3 weeks. In particular, irofulven may be administered at a treatment regimen of about 0.45 mg/kg on day 1 and day 8 every 3 weeks. The treatment regimen may be repeated one to five times, one to ten times, one to fifteen times, one to twenty times, or more. The administration of irofulven can be repeated at such a frequency for a certain period of time, followed by a period without treatment. Such repeated administrations can occur over a course of therapy lasting a specified length of time (e.g., at least 1 week, 2 weeks, 3 weeks, 1 month, 2 months, 3 months, 6 months, 8 months, 10 months, 12 months, 18 months, 24 months, 36 months, 48 months, or 60 months).

Irofulven can be administered in a pharmaceutical composition that includes one or more pharmaceutically accept-

able carriers, excipients, or diluents. Examples of suitable carriers, excipients, or diluents of irofulven include, e.g., saline, sterile water, polyalkylene glycols, oils of vegetable origin, hydrogenated naphthalenes, suitable buffer, 1,3-butanediol, Ringer's solution and/or sodium chloride solution. Exemplary formulations for parenteral administration can include solutions prepared in water suitably mixed with a surfactant, e.g., hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, DMSO and mixtures thereof with or without alcohol, and in oils. Under ordinary conditions of storage and use, these preparations may contain a preservative to prevent the growth of microorganisms. Other exemplary carriers, excipients, or diluents are described in the Handbook of Pharmaceutical Excipients, 6th Edition, Rowe et al., Eds., Pharmaceutical Press (2009), hereby incorporated by reference in its entirety.

Kits

Kits of the invention can be used for determining the responsiveness of a cancer patient (e.g., a patient having a solid tumor cancer, such as prostate cancer, ovarian cancer, or hepatocellular carcinoma (HCC), or a hematological cancer, such as lymphoma (e.g., cutaneous T-cell lymphoma (CTCL)) to irofulven. Kits of the invention can include reagents and/or materials for, e.g., collecting and/or purifying nucleic acids from biological samples (such as those obtained from a patient to be treated with a target drug(s) of the invention), reagents for amplifying such nucleic acids to produce an amplified sample, and/or at least one device of the invention. Reagents for amplifying nucleic acids may include, e.g., PCR reagents, including but not limited to DNA polymerase, RNA polymerase, PCR buffer, magnesium chloride solutions, nucleic acid primers (e.g., primers designed to target particular biomarkers of responsiveness to a target drug(s) of interest), and/or any other PCR reagents as are well known in the art. In particular, kits useful in the method may include includes one or more of the following: a kit for RNA extraction from tumors (e.g., Trizol for mRNA, mirVana miRNA isolation kit from Ambion Inc), a kit for RNA labeling (e.g., MessageAmp from Ambion Inc., FlashTag from Genisphere Inc), a microarray for measuring biomarker expression (e.g., HG-U133A, HG-U133_Plus2 or miRNA-1.0 from Affymetrix Inc), a microarray hybridization station and scanner (e.g., GeneChip System 3000Dx from Affymetrix Inc), and/or software for analyzing the expression of biomarker genes or RNAs (e.g., miRNAs) as described in herein (e.g., implemented in R from R-Project or S-Plus from Insightful Corp.).

For example, a kit of the invention can include one or more probes capable of detecting one or more biomarkers of Tables 1-4 (e.g., the kit may include probes for the biomarkers of Tables 1-4). Such probes can, for example, include nucleic acids capable of hybridizing to the biomarker based on nucleic acid sequence complementarity. In particular, a probe has at least 85% sequence identity (e.g., 85%, 90%, 95%, 97%, 98%, 99%, or 100% sequence identity) to a nucleic acid sequence that is complementary or identical to at least 5 (e.g., at least 15) consecutive nucleotides of one or more biomarkers. The probes can be attached a solid surface, such as a microarray. The kit may include NanoString capture probes, NanoString reporter probes, and/or one or more nCounter cartridges. The kit may include reagents for next generation sequencing, including but not limited to poly(T) oligonucleotides, dye terminators, sequencing adapters, adapter ligation reagents, reverse transcriptase, primers (e.g., random primers), DNA-cleaving enzymes, polymerases, and/or any combination thereof. The kit may

also be one that includes a protein array and/or reagents for detection of the polypeptide product(s) of one or more biomarkers of Tables 1-4.

The following examples are intended to illustrate, rather than limit, the invention.

EXAMPLES

Example 1

Identification of Biomarkers of Sensitivity and Resistance to Irofulven Using Affymetrix HG-U133A Arrays

DNA chip measurements of the 60 cancer cell lines of the NCI60 data set were performed using Affymetrix

HG-U133A arrays and logit normalized. For each array, the logit transformation was performed followed by a Z-transformation to mean zero and SD 1, and correlated to growth inhibition (log(GI50)). Growth inhibition data of irofulven against the same cell lines were downloaded from the National Cancer Institute. Each gene's expression in each cell line was correlated to the growth of those cell lines (log(GI50)) in the presence of irofulven. The Pearson correlation coefficient was then determined to identify genes positively and negatively correlated to sensitivity to irofulven. Tables 1 and 2 show the top positively correlated genes (the biomarkers of sensitivity) and negatively correlated genes (the biomarkers of resistance) using the Affymetrix HG-U133A arrays.

TABLE 1

Biomarkers of sensitivity to irofulven. Dashes indicate that the Affymetrix probeset has not been mapped to a specific gene. Affymetrix IDs refer to the array type HG-U133A.

Gene	Affymetrix ID	Correlation	Affymetrix Probe Sequence	Affymetrix Probe SEQ ID NO:
S100A10	200872_at	0.571	AGAGTTGTCCAAGGGTCGCTTAAG	1
ATP1B1	201242_s_at	0.554	TGATCACAAGCACAAATCTTTCCCA	2
CTBP2	201220_x_at	0.549	ACACCCTGCTCTACAATGTTGCATC	3
ASPH	209135_at	0.539	AAAGCTGTGCTGTCGGTGATACAGA	4
LAPTM4B	214039_s_at	0.525	GTTACAAAGTCAGCAACTCTCCTGT	5
CTBP2	210835_s_at	0.524	TGCACGCATAGGATTGAAGACAGTA	6
MYOF	201798_s_at	0.519	CCAGTAGCAGGTTACGCCATGTCAC	7
TJP1	202011_at	0.518	AATACACCACTACATTCTGTTAATC	8
ASPH	210896_s_at	0.517	GTAACGCCTTGAGCTGGGTTGATTG	9
LPP	202822_at	0.511	GTTTGGTGCACTCTCGTGGGAGACA	10
PFN2	204992_s_at	0.503	CCCCAGGGACATTCATCATTGCAA	11
ACTN1	208636_at	0.499	CAAGCACAAAGTTATATTCCATCCT	12
CKAP4	200999_s_at	0.474	TGTGTAATTGTTTGCTGTATCTCCC	13
MYOF	211864_s_at	0.46	TACCAAATCGACCAGAAACCTCCTT	14
PPIC	204517_at	0.455	CACCTGCTTAGGGACTTTGAACTTA	15
MET	203510_at	0.454	AAACTTGTCCCTTAGATTAATGTGTC	16
CEBPD	203973_s_at	0.454	AAGCGGCGCAACCAGGAGATGCAGC	17
PAPSS2	203060_s_at	0.452	GATTTCAAGCTGTTCTGAGACATCT	18
UGDH	203343_at	0.448	TTAATTTCCAGTCACCCCAAATATG	19
FKBP9	212169_at	0.448	AACAAGGTGACATTTTTCTGCTGCC	20
NQO1	210519_s_at	0.446	GTGGCTTCCAAGTCTTAGAACCTCA	21
EGFR	201983_s_at	0.443	AAAATCCAGACTCTTTGATACCCA	22
LAPTM4B	208767_s_at	0.44	AACTTCCCCAAATCTGATGGACCT	23
RBPM5	209488_s_at	0.44	AATTCGCAAACTACGACTAGAG	24
ANXA2	210427_x_at	0.439	CGTGGCCATCCCTGTGAGGGTGACG	25
NQO1	201468_s_at	0.435	TTCATCTTCACTGCAATTTTGTGTA	26
LAPTM4B	208029_s_at	0.433	ACATGGGGTGACATGCCTCGTATGT	27

TABLE 1-continued

Biomarkers of sensitivity to irifolven. Dashes indicate that the
Affymetrix probeset has not been mapped to a specific gene.
Affymetrix IDs refer to the array type HG-U133A.

Gene	Affymetrix ID	Correlation	Affymetrix Probe Sequence	Affymetrix Probe SEQ ID NO:
ANXA2	213503_x_at	0.433	CTCACCATGCTTCCAGCTAACAGGT	28
ANXA2	201590_x_at	0.43	GAGGGTGACGTTAGCATTACCCCA	29
SEPT10	212698_s_at	0.43	TGATGACTTCATGCTTTATTATGCC	30
ALCAM	201952_at	0.425	ACAGCTGTCAGAACCTCGAGAGCAG	31
NQO1	201467_s_at	0.423	TCTCTGCAAGGGATCCACGGGGACA	32
SKAP2	204362_at	0.422	GCAAATGGCAGTGTGCTGTACCTG	33
CAPN2	208683_at	0.422	GACACGAGGCCCTTGGCAGGAATA	34
RCN1	201063_at	0.42	ACAATGCATTTCTCAGTGATCACT	35
TXNRD1	201266_at	0.418	ACACGTGCTTGTGGACATCAGCCTC	36
ACTN1	208637_x_at	0.418	GGCGCTGTACGGCGAGAGTGACCTC	37
CALM1 CALM2 CALM3	209563_x_at	0.416	TGGCCAGTTTTTCATGCATGCAGCT	38
LAMB1	201505_at	0.412	AAGAGTCAGCTGATGCCAGAAGGAA	39
CTSL1	202087_s_at	0.411	GAAACCATTGTGGAATTGCCTCAGC	40
TGIF1	203313_s_at	0.41	ACTTACAGCTTAACCCATTTCAAG	41
ANXA2P2	208816_x_at	0.41	AAGCCCTTGTATTTTGTCTGATCAGC	42
CALM1 CALM2 CALM3	200653_s_at	0.408	GAAGAAATCCGTGAGGCATTCCGAG	43
CD24	209771_x_at	0.403	GAACACTCTTGCTTTATTCCAGAAT	44
CALM1 CALM2 CALM3	211984_at	0.403	AATTTGGTCAAGTCTACTCTCCGT	45
PLXNB2	208890_s_at	0.397	AGAAAAAGCGGTACGATGCCTTCCT	46
SDC4	202071_at	0.396	CAGTAACCACATGCGGCTGTTTAAA	47
ACTN4	200601_at	0.394	TAACCAAGGAGGGGCCAGTGGATTC	48
TNFRSF12A	218368_s_at	0.389	AACACTAGGGGCTGGCCACTAGGA	49
LOC100652886 LOC100653157 TGFB1	201506_at	0.386	CTTTTATGGGGCCCTGTCCAGGTAG	50
SQSTM1	201471_s_at	0.385	CTGCCTTCTTCCAGGATCAGGGGTT	51
CD24	216379_x_at	0.384	AATAGACACTCCCCGAAGTCTTTTG	52
ALDH7A1	208951_at	0.381	ACACAGAGACTTTTGCTCCGATTCT	53
LIF	205266_at	0.379	GTAGCATTTCCCTGCAGATGGTACA	54
AMOTL2	203002_at	0.377	TTTTTAGTTCTCCTTGATTCTTTGT	55
MYO1B	212364_at	0.377	ATGACCAGGTTAAATCCCTCTACAT	56
CDC42BPA	214464_at	0.377	AGCTCTGCAGTATTCAACTGTTGAT	57
CCND1	208712_at	0.374	AACCAAAGAATTTGCACCCCGCTG	58
AGRN	212285_s_at	0.374	GAGCTCACTGTGGGATGGGGTTGAC	59

TABLE 1-continued

Biomarkers of sensitivity to irifolven. Dashes indicate that the
Affymetrix probeset has not been mapped to a specific gene.
Affymetrix IDs refer to the array type HG-U133A.

Gene	Affymetrix ID	Correlation	Affymetrix Probe Sequence	Affymetrix Probe SEQ ID NO:
CD24	266_s_at	0.373	GTAATCTAATATGGCCACAGTAGTC	60
CD24	208651_x_at	0.372	AATAGCCACATTTAGAACACTTTTT	61
CD24	208650_s_at	0.371	AATCTGCTGGAGTTTCATGTACAAG	62
RBPMS	209487_at	0.37	AATTAGATTTGTCTCTGGGAATGTG	63
CALM1 CALM2 CALM3	200655_s_at	0.368	AACCATCAACATTGCTGTCAAAGA	64
LGALS3	208949_s_at	0.367	CACTTTAACCCACGCTTCAATGAGA	65
CALM1 CALM2 CALM3	211985_s_at	0.367	TCGGCAACTTACACACATTGAAAAT	66
PPP1R3C	204284_at	0.365	TGTACACAACCTCACATCCTTCATAT	67
LMNA	212086_x_at	0.362	TTCGGGGACAATCTGGTCACCCGCT	68
ADAM9	202381_at	0.361	ATCTGAACTTTCAAAGCTTGCTATT	69
FZD6	203987_at	0.361	GAGTGTCCACTATTGATTGTATTAT	70
TMSB10	217733_s_at	0.361	GCAGGAGAAGAACACCCTGCCGACC	71
AMIGO2	222108_at	0.359	ATATTGGTTCATGTGCTTGTGTATA	72
PLK2	201939_at	0.358	AGCTTTTGGCTGCGTAACTGTGAAC	73
NFIB	209289_at	0.357	TGAACGAATTTATTTTCCCCTCAGT	74
ULK2	204062_s_at	0.355	ACAGTTCACCAAATAGCTAGTCATG	75
AVPI1	218631_at	0.354	CATTTCACTACTCATGCTACTAATC	76
CYR61	201289_at	0.353	GTGGAGTTGATGACTTCTGTTTTC	77
EXT1	201995_at	0.353	GGCCAATGAGAACTCAACTCCTGGC	78
TM4SF1	209386_at	0.353	AAAGCCTTTTGTCTCCAAAGATGA	79
COTL1	221059_s_at	0.351	TGCAAGCTGCGAGGATGGCTTGGGC	80
PRSS23	202458_at	0.35	GAGGGGTGACACAGTGTCCCTCCT	81
YES1	202933_s_at	0.348	AGCTTTTCGTCTTCAGTGTCTTAAT	82
G6PD	202275_at	0.347	CCAGAGCTTATTGGCCACTGGGTCT	83
BASP1	202391_at	0.347	CATCTCCTCTCCAGATATTTTGG	84
ZFP36L1	211962_s_at	0.347	ATGGTTTTTGTCTTAGAATACCGTA	85
FAIM	220643_s_at	0.345	GGACCAAAGTCACTAATGTTTTACA	86
FLNB	208614_s_at	0.344	TCAGCCTGGGCAGTCTTACCAAAAT	87
CAV2	203323_at	0.343	CCTAGGCCATTGCAGCATCCTTAGA	88
ABCC3	208161_s_at	0.343	CACCCCTAGGAACTCAGTCTGTAC	89
MIR21 VMP1	220990_s_at	0.342	TAAGGTAAGGTATCCACCCTCGATG	90
FTH1	214211_at	0.341	TAGAACTAAGGGTTCCCGACTCTGA	91
PLOD2	202620_s_at	0.34	TCCATTTTATTCTTCTGAGTGTCTA	92
MXRA7	212509_s_at	0.34	CAGCATCAACCCCTATGGCATGCAT	93

TABLE 1-continued

Biomarkers of sensitivity to irifolven. Dashes indicate that the Affymetrix probeset has not been mapped to a specific gene. Affymetrix IDs refer to the array type HG-U133A.

Gene	Affymetrix ID	Correlation	Affymetrix Probe Sequence	Affymetrix Probe SEQ ID NO:
ANXA4	201301_s_at	0.339	AAAGTACTGCTTGTCTCTGTGGAG	94
PYGL	202990_at	0.339	AGAGAACCTGTTTCATCTTTGGCATG	95
OLFML2A	213075_at	0.338	CCAATTGTGCTGAGTCTCCTACTAG	96
CYP1B1	202437_s_at	0.336	TAGCCTTTACTGTTTGATATACCAA	97
CAMSAP2	212765_at	0.335	GAGCATTGCTTACAGGTTTTTTGTT	98
GOLM1	217771_at	0.335	TGGGGCCTAGAAGTTACAGAGCATC	99
IER3	201631_s_at	0.334	GAGACTTCGGCGGACCATTAGGAAT	100

TABLE 2

Biomarkers of resistance to irifolven. Dashes indicate that the Affymetrix probeset has not been mapped to a specific gene. Affymetrix IDs refer to the array type HG-U133A.

Gene	Affymetrix ID	Correlation	Affymetrix Probe Sequence	Affymetrix Probe SEQ ID NO:
IGJ	212592_at	-0.609	GCTCACCTGAAAGAGGTATGCTCTC	101
MZB1	221286_s_at	-0.608	AAAGAAGCTGGGGCTTGCTCTGACG	102
CD8B	207979_s_at	-0.59	GTAACATTGGGTCTGGTCTTTCA	103
ITGB7	205718_at	-0.588	GAGGATGACGCCAGAGGCACGGTCG	104
CD28	206545_at	-0.582	GATCAAACCTCAGCAGTACTTGGGTG	105
CD53	203416_at	-0.573	AAAGGGCAAGATCTCATTTCAATTT	106
IQGAP2	203474_at	-0.567	ACTGTGATATAGGTACTCTGATTTA	107
HCLS1	202957_at	-0.554	GTACGTCTAGATTGTGTGGTTTGCC	108
CD37	204192_at	-0.536	CAACGACTCCACAATCCTAGATAAG	109
ICAM3	204949_at	-0.527	GTACCCCGAGCTGCGGTGTTTGAAG	110
PIM2	204269_at	-0.526	ACCGGACACCACCAGACAATAGGAT	111
ICAM2	213620_s_at	-0.516	CTTGGGACATTGCCTTTTCTAGCCC	112
ICAM2	204683_at	-0.512	CAAACACTCAGCCCCGAAGATGTTG	113
GLYR1 SEPT6	212414_s_at	-0.509	ATGTGGCTGTTAATATGTGCTTGTT	114
CORO1A	209083_at	-0.504	GATCGCCAGGTTCTACAAGCTGCAC	115
SLC43A3	213113_s_at	-0.498	CTTTAGGCCTGTTTGGCTCCGAAGC	116
NFATC3	210555_s_at	-0.497	TTGTGTGATCCAGCGTCATTTCCAC	117
SSBP2	203787_at	-0.493	GTATATGTCTGCAATCATGGATAGG	118
PTPN7	204852_s_at	-0.492	GGGTACAAGCTCCAGAACAGTAACC	119
NCKAP1L	209734_at	-0.486	GTGGAAGCTGTGGTCACTTTCGCAG	120
RHOH	204951_at	-0.474	GAGGCTTGGCCACTGGATGTTTTCA	121
MYB	204798_at	-0.465	TGTGGTTGATAGCCAGTCACTGCCT	122

TABLE 2-continued

Biomarkers of resistance to irifolven. Dashes indicate that the Affymetrix probeset has not been mapped to a specific gene. Affymetrix IDs refer to the array type HG-U133A.

Gene	Affymetrix ID	Correlation	Affymetrix Probe Sequence	Affymetrix Probe SEQ ID NO:
LCP1	208885_at	-0.462	TTTGGAGGCAATCCTACCTTGCTTT	123
ARHGAP15	218870_at	-0.458	ACCTCATGTCCACGCAAAGCTTGGG	124
LRMP	204674_at	-0.454	AGTGGGATGTCTCTTCAGTTTATGA	125
FARSA	216602_s_at	-0.453	TGGTGGGCCACAAGGTGAACCTGCA	126
SEPT6	212415_at	-0.452	TAACCACCGATCAGCACAGCTGTCC	127
LAPTM5	201721_s_at	-0.448	CATAGGCGAATCTGTTCTGCCCGAG	128
EVI2B	211742_s_at	-0.447	ACATATACTTATTACCCAGTACAGT	129
USP7	201498_at	-0.439	GAACATGTACAATTTGCCACTGGGA	130
CCND2	200953_s_at	-0.436	ATGTTGTATTGGCTATGATGGTGAC	131
SEPT6	213666_at	-0.435	AAAGGTGTGACCAGTCATTGCCCT	132
RNASE6	213566_at	-0.433	ATTTCTAACCTGCAACTTTTGCCA	133
MYC	202431_s_at	-0.432	AAAAGCCACAGCATAACCTGTCC	134
CYTIP	209606_at	-0.431	AAATCTTAGGTTTGCTTATGCCAG	135
HBA1 HBA2	209458_x_at	-0.429	AGAGAACCACCATGGTGTGTCTC	136
EVI2A	204774_at	-0.428	AATTTAATGGTATCTTCCTTGCTGG	137
NARF	219862_s_at	-0.428	CGGAGAGGTGGTGTACGCTTTGCT	138
LAPTM5	201720_s_at	-0.426	AGCTGCTCACAACTGGGTCAACGCT	139
MFNG	204153_s_at	-0.426	GGTCCCAGCCAATTGTGATGATCCT	140
ARHGDIB	201288_at	-0.424	GTCACTCAACGTGGTCCCTAGAACA	141
ZFP36L2	201369_s_at	-0.422	GACGACTGAGGCAAGAGGGCGCCAG	142
MAGEA9 MAGEA9B	210437_at	-0.42	GGTTCCTTGTCTATTGGGTGATTTG	143
NASP	201970_s_at	-0.417	GTGACTGATATTTCCACCTTGTC	144
SMARCC1	201074_at	-0.414	GAAGAAGGCCTAATCTCTCTTTT	145
ARHGAP6	206167_s_at	-0.413	AAGTGCATAACTATTTTGACCAGC	146
PTP4A3	206574_s_at	-0.413	TGGCATCACCGTTGTGGACTGGCCG	147
SAMSN1	220330_s_at	-0.411	TGGACACATTTTATCCTGATCCACA	148
HBA1 HBA2	211745_x_at	-0.409	TGGCGAGTATGGTGGGAGGCCCTG	149
CXCR4	211919_s_at	-0.409	GTGGTCTATGTTGGCGTCTGGATCC	150
FEN1	204767_s_at	-0.408	TGGACCTAGACTGTGCTTTTCTGTC	151
HBA1 HBA2	204018_x_at	-0.405	CTGACCTCCAATACCGTTAAGCTG	152
HBA1 HBA2	211699_x_at	-0.402	CGCACAAGCTTCGGGTGGACCCGGT	153
SLC19A1	211576_s_at	-0.401	GATGTGATGTGAATACTCTCCAC	154
ARHGEF3	218501_at	-0.399	TCATGTGCATTCAAGCTGTGTGACA	155

TABLE 2-continued

Biomarkers of resistance to irifolven. Dashes indicate that the Affymetrix probeset has not been mapped to a specific gene. Affymetrix IDs refer to the array type HG-U133A.

Gene	Affymetrix ID	Correlation	Affymetrix Probe Sequence	Affymetrix Probe SEQ ID NO:
CXCR4	209201_x_at	-0.398	AGCACATCATGGTTGGCCTTATCCT	156
UTP3	209486_at	-0.397	GAAATTCGTCATCTGTTGACACTTA	157
PDSS1	220865_s_at	-0.396	GCAGCTATCTTACCAGACTGTGCCT	158
MAZ	207824_s_at	-0.395	AAATGTGAGGCAGCTTTCGCCACGA	159
SELPLG	209879_at	-0.395	CACTGCACTGCCATTGTCTTTTGGT	160
FARSA	202159_at	-0.394	TCCTGTGTGGTGTGTCTACTGTGAG	161
LCP2	205269_at	-0.394	TGTTTTTTACAGCCAAACCTCTGTC	162
STAT5A	203010_at	-0.393	CCTCCCTCTGAGGCGTGAGGACTCG	163
CISH	221223_x_at	-0.392	AAAGCCCATCCTGAGACATCTTGCT	164
MANIA1	221760_at	-0.391	GGTTTTCATATGAGCTACACATTGT	165
HBA1 HBA2	217414_x_at	-0.388	TCAAGGCCGCCTGGGGTAAGGTCGG	166
TCF4	222146_s_at	-0.388	AACAGCTGTATTATCTTAAACCCAC	167
LAIR1	210644_s_at	-0.385	CAGTTCCCTGGCTGTTTCTAGAGAC	168
MYLIP	220319_s_at	-0.382	AGCTACGCAAGCTGAAGGAAGCCAT	169
IKZF1	205039_s_at	-0.38	CGCCCATCCGTGCTATGACATGGAG	170
CXCR4	217028_at	-0.379	GTATGTCTCGTGGTAGGACTGTAGA	171
TAPBPL	218747_s_at	-0.377	GAACAGCCTTGGGAGTCATCTTTGC	172
ZFP36L2	201368_at	-0.376	GTGAAGCAACCGCCTTAGTGCTGAA	173
IL2RG	204116_at	-0.374	AACCCCAATCCTCTGACAGAAGAAC	174
TNFAIP8	210260_s_at	-0.374	GTGTCATTGCCTTGAAATGCTTGCT	175
PRKCB	209685_s_at	-0.372	GAAAAGGGCATTGGCACCCTCTC	176
PAICS	201014_s_at	-0.371	GATGTCTGGGAACACTGCATATCCA	177
IKZF1	205038_at	-0.371	CCCATATCCCTTCTGTAATTTGTAC	178
EZH2	203358_s_at	-0.368	CTGCCTTAGCTTCAGGAACCTCGAG	179
ADCK3	218168_s_at	-0.368	CCCTTCCAATCTCTGTTTCTAGTCAA	180
SRSF2	214882_s_at	-0.365	AGTGCAGAGTGCTTGGCTGTTTCTC	181
VAR5	201797_s_at	-0.364	TGAGCTGGCGCTAAGCATCACGCGA	182
NDUFV1	208714_at	-0.364	GACGGTGCTGATGGACTTCGATGCG	183
REPIN1	219041_s_at	-0.363	CCTATAATTTCTACCTATTGGGCCT	184
GMFG	204220_at	-0.362	GGCTGGGGACTGAATTCCTGATGTC	185
MCM7	208795_s_at	-0.357	GTCAAAGGACTCTCTTCTAGGAGAC	186
TUFM	201113_at	-0.356	ATGCCCGGGGAGGACCTGAAGTTCA	187
HMHA1	212873_at	-0.355	CTCCCTTTTCCAGAACCAGGTGT	188
SON	213538_at	-0.355	TTGGGTACATAGCCCATTGCCCTTA	189
TXNIP	201008_s_at	-0.353	TACAAGTTCGGCTTTGAGCTTCTC	190
NPRL2	203246_s_at	-0.353	GACTCGGGAAGAGCAGAGCCACCCT	191

TABLE 2-continued

Biomarkers of resistance to irifolven. Dashes indicate that the Affymetrix probeset has not been mapped to a specific gene. Affymetrix IDs refer to the array type HG-U133A.

Gene	Affymetrix ID	Correlation	Affymetrix Probe Sequence	Affymetrix Probe SEQ ID NO:
TCF4	213891_s_at	-0.353	GGGAAATTTTTTGCCTGTACACA	192
NADK	208918_s_at	-0.352	ATTTTTCCGCAAATCAGTCGGTTGA	193
RRP1B	212846_at	-0.352	TGTTATCCTTTCTAATTTTACTGA	194
MAP4K1	214219_x_at	-0.352	CCAGCAACCTCTACATCCAGGAATG	195
DDX39A	201584_s_at	-0.35	GCAGTTCAAGGATTTCCAGCGCGG	196
MAP4K1	206296_x_at	-0.35	GGTCAGCTTCAGGCCTTCTGGAAGC	197
TXNIP	201009_s_at	-0.349	GAAGCAGCTTTACCTACTTGTCTTCT	198
USP20	203965_at	-0.348	GCGTCTTTGTTTCTATCAGTCTTTG	199
IFI16	208965_s_at	-0.347	GACCTGGCTGAACTCTTAAAAAAG	200

Example 2

Identification of Biomarkers of Sensitivity and Resistance to Irifolven Using Affymetrix HG-U133_Plus_2 Arrays

DNA chip measurements of the 60 cancer cell lines of the NCI60 data set were also performed using HG-U133_Plus_2 arrays and logit normalized. For each array, the logit transformation was performed followed by a Z-transformation to mean zero and SD 1, and correlated to growth inhibition (log(GI50)). Growth inhibition data of irifolven against the same cell lines were downloaded from the National Cancer Institute. Each gene's expression in each cell line was

25

correlated to the growth of those cell lines (log(GI50)) in the presence of irifolven. The Pearson correlation coefficient was then determined to identify genes positively and negatively correlated to sensitivity to irifolven. Tables 3 and 4 show the top positively correlated genes (the biomarkers of sensitivity) and negatively correlated genes (the biomarkers of resistance) using the Affymetrix HG-U133_Plus_2 arrays. The Affymetrix HG-U133_Plus_2 array includes additional genes (e.g., PTGR1 and NME7) that are not included in the Affymetrix HG-U133A array, which were top ranking biomarkers of sensitivity and biomarkers of resistance, as shown in Tables 3 and 4.

TABLE 3

Biomarkers of sensitivity to irifolven. Dashes indicate that the Affymetrix probeset has not been mapped to a specific gene. Affymetrix IDs refer to the array type HG-U133_Plus_2.

Gene	Affymetrix ID	Correlation	Affymetrix Probe Sequence	Affymetrix Probe SEQ ID NO:
ATP1B1	201242_s_at	0.33	GGACCTACACTTAATCTATATGCTT	201
UCHL1	201387_s_at	0.3	AGCCCATGATGCCGTGGCACAGGAA	202
PTGR1	231897_at	0.3	AGGATTTGAAAACATGCCAGCTGCA	203
NME7	227556_at	0.29	GACACAGCTTTAGAACATAACCGGAG	204
PLS3	201215_at	0.27	TGTACTCTTGCTTTGTCAAGCTGTT	205
S100A10	200872_at	0.27	GGACCTGGACCAGTGTAGAGATGGC	206
CD24	209771_x_at	0.27	GAACCTGGTCCTAAGCCTAAAAGTG	207
NQO1	210519_s_at	0.26	ATATAGCATTGGGCACACTCCAGCA	208
CD24	216379_x_at	0.26	CATGGTCACACACTGATGCTTAGAT	209
PTGR1	228824_s_at	0.26	AATGGAGAGGTCCTGCTTGAAGCTT	210
MYOF	201798_s_at	0.26	CCAGTAGCAGGTTACGCCATGTCAC	211
LAPTM4B	214039_s_at	0.26	ATATTTGATATACTTCTGCCTAACA	212
CALD1	212077_at	0.25	ATCACTGCTGACTTTTATTCCAATA	213

TABLE 3-continued

Biomarkers of sensitivity to irifolven. Dashes indicate that the Affymetrix probeset has not been mapped to a specific gene. Affymetrix IDs refer to the array type HG-U133 Plus 2.

Gene	Affymetrix ID	Correlation	Affymetrix Probe Sequence	Affymetrix Probe SEQ ID NO:
PDGFC	218718_at	0.25	AAGTAGACATTCAGATCCAGCCATT	214
BASP1	202391_at	0.25	TGGATCTCAATGCCAATCCTCCATT	215
NQO1	201468_s_at	0.25	AATAGTCAATTTCTACTTCTGGAAG	216
ID1	208937_s_at	0.25	CACCCTCAACGGCGAGATCAGCGCC	217
GJA1	201667_at	0.25	GAGTGGACTATTAATGTGCCTAAA	218
ATP1B1	201243_s_at	0.25	GTTATGCTTGTATTGAATGCTGTCT	219
CD24	208650_s_at	0.24	GAGAGGTTTGACTAGATGATGGATG	220
EGR1	227404_s_at	0.24	TGAGCATGTCCCTCACAATTGCACA	221
PERP	222392_x_at	0.24	GTGCCACTAAAACAGCCTCAGGAGA	222
CYR61	201289_at	0.24	CTTCATTTTGGAGCTTGTGGAGTTG	223
AKR1B10	206561_s_at	0.24	GCAACCATACTCAGCTTCAACAGAA	224
PFN2	204992_s_at	0.24	TTGCTTCTATTGTTTGGGCCTTGTG	225
TFPI2	209278_s_at	0.23	GCTTTCACCTATACTGGCTGTGGAG	226
CTBP2	201218_at	0.23	GAGCCTTTGTATAGGTACATTCCTG	227
ASPH	209135_at	0.23	AGTAAGTTTTGCTGGATTTTTGTAG	228
PLK2	201939_at	0.23	CAGTTCCTGACTTTGGACAATCCCA	229
FAM213A	228155_at	0.22	CATATGATGTTTGAGTGCTGTTGTT	230
NQO1	201467_s_at	0.22	CATTCTCTGGCCAATTCAGAGTGGC	231
MYOF	211864_s_at	0.22	TACCAAATCGACCAGAAAACCTCCTT	232
TM4SF1	209386_at	0.22	AAAGCCTTTTGTCTCCAAAGATGA	233
ALCAM	201952_at	0.22	GGCAGCCACATGCACGAAGATGCTA	234
WWTR1	202133_at	0.22	CCATTTCTTTCCTGATTACACCAT	235
EDIL3	225275_at	0.22	ATAACCTTTGCAAACCTTCAAGCTG	236
COL1A1	1556499_s_at	0.22	TTTTTATCTTTGACCAACCGAACAT	237
TJP1	202011_at	0.22	GATACAATGCTGTGCCCTAAAGTGT	238
PLOD2	202620_s_at	0.22	TGTTGACTTGATGTTTTATCACTTC	239
YAP1	224894_at	0.22	ACACAGGGAAGTGACTTTGCTACAA	240
EGFR	201983_s_at	0.21	GTGTCAACAGCACATTCGACAGCCC	241
MET	203510_at	0.21	GCTGAACGAATGGTACTTCGTATG	242
AJUBA	225806_at	0.21	AAAGCTCAATTCCTATTTTGGTGTG	243
CEBPD	203973_s_at	0.21	AGAAGCTACAGCCTGGACTTACCAC	244
ASPH	210896_s_at	0.21	CGCTCAGTGCTCTTACTAGATGAAC	245
AMIGO2	222108_at	0.21	GAGTAACTTCTTAAATCCCTGTTCT	246
AKR1C1	204151_x_at	0.21	ATCTCTCCTGCTTGGTGATTTTCAGC	247
AKR1C2	209699_x_at	0.21	CACATCGCCTCTGGTTAAATCTCTC	248
LOC101930400				

TABLE 3-continued

Biomarkers of sensitivity to irifolven. Dashes indicate that the Affymetrix probeset has not been mapped to a specific gene. Affymetrix IDs refer to the array type HG-U133 Plus 2.

Gene	Affymetrix ID	Correlation	Affymetrix Probe Sequence	Affymetrix Probe SEQ ID NO:
AKR1C3	209160_at	0.21	CAGTCAACTACAGCTGAGTCCATAG	249
LAPTM4B	208767_s_at	0.21	TTCACCTAACCTCCCTAGGCATTGA	250
PRSS23	202458_at	0.21	AGAATCACTCCTCTCAAATATGCCC	251
CKAP4	200999_s_at	0.21	CCATGAAGAGGTTTGCCGTCTGGGC	252
GPX8	227628_at	0.21	GAGCACTGTGTATGACTGAAATTC	253
LOC101928916 NNMT	202237_at	0.21	CAACAACGAAGGACTTTTCTCCCTG	254
LAMC1	200771_at	0.21	TCACCTTAGCTGTTGCCTTACTCT	255
TGFBI	201506_at	0.21	AGAACTTGGATGTCACTGCCTGAC	256
LAPTM4B	208029_s_at	0.2	AAGACCATTAGAAAGCACCAGGCCG	257
CD24	266_s_at	0.2	CTACTGTGTGTGAATGAACACTC	258
PERP	217744_s_at	0.2	TTCTACACATCTGCCTAACTGGGA	259
AKR1C2 LOC101930400	211653_x_at	0.2	CCCCCTAATTATCCATTTTCTGAT	260
YAP1	224895_at	0.2	GTTTTATGTCCTTGTTCCTAATGTA	261
ABCC3	208161_s_at	0.2	CACCCCTAGGAACTCAGTCTGTAC	262
LIMCH1	212328_at	0.2	TGGGTTCTTTGCATGTGGTTCCAT	263
KRT19	201650_at	0.2	GCTGAGCATGAAAGCTGCCTTGAA	264
CD24	208651_x_at	0.2	AACACTTTTTGTTATCAGTCAATAT	265
CRIM1	228496_s_at	0.2	TAAAGTTCAGCAACCTCTGTCCAAG	266
SEMA3C	203789_s_at	0.2	GTGACTTAATATCTATTCCATTTGT	267
TRIM16	204341_at	0.2	ATATGGTGCTGTCTCTATGTGTTT	268
TSPAN6	209108_at	0.2	CTTGGGTCTAAGGCATCCACGACTG	269
PTPN14	226282_at	0.2	TCACCATCTTATGTTGTTGCCGT	270
NGFRAP1	217963_s_at	0.2	CAAGTGGGTCTTGTGTGCCAGCTT	271
SLPI	203021_at	0.19	TCTGTCTCCTAAGAAATCTGCCCA	272
LGALS3	208949_s_at	0.19	CACTTTAACCACGCTTCAATGAGA	273
CTBP2	210554_s_at	0.19	GCACCCCAACGAGCAATAGCAGAGA	274
C19orf33	223631_s_at	0.19	TTCTCTTACCGCCATGGAGTTGAC	275
PLOD2	202619_s_at	0.19	CTTAATGTCTGCTGAGCCTTAAA	276
PPIC	204517_at	0.19	CCCTTCCTCAAGTGGTGTATTTTA	277
ERRFI1	224657_at	0.19	GGTACATTACTGCAATGTTCTCTTA	278
CTBP2	201220_x_at	0.19	GTTTGCTGTGGTAGACACCTGCAC	279
NARR RAB34	1555630_a_at	0.19	AATGCATTGCATCAACCTACTATAG	280
FAM213A	224435_at	0.19	AAACCACAGACTTTGGCCTCAGAGA	281
SEPT10	212698_s_at	0.19	ATAAAGTACCTTTGAGCATGAGTGT	282
LAPTM4B	1554679_a_at	0.19	GGTCCTTATTATCTTCTGTTTATT	283

TABLE 3-continued

Biomarkers of sensitivity to irifolven. Dashes indicate that the Affymetrix probeset has not been mapped to a specific gene. Affymetrix IDs refer to the array type HG-U133 Plus 2.

Gene	Affymetrix ID	Correlation	Affymetrix Probe Sequence	Affymetrix Probe SEQ ID NO:
PON2	201876_at	0.19	GACTACTATGGCTGTTTAGAACTAC	284
CD24	209772_s_at	0.19	TGGAAGCTCAAGTAACTCCTCCCAG	285
TPM1	210986_s_at	0.19	ATTCCTTTCTGATTGGCACACGTGC	286
RAB13	202252_at	0.19	ACTAGGGAATTTGCTCCTGTTCTGT	287
AKR1C1	216594_x_at	0.19	TGTGGTCCTGGCCAAGAGCTACAAT	288
PTK2	208820_at	0.19	AAAGCCATGTTGACTATTTTACAGC	289
LAMB1	201505_at	0.18	AAAGCTCAAGAATTAGCAAGACTGG	290
GPRC5A	203108_at	0.18	TCCCCAACTTGCTGTCAATTCCGA	291
PAPSS2	203060_s_at	0.18	GATTTCAAGCTGTTCTGAGACATCT	292
LPP	241879_at	0.18	TAAACAGCCACAATCGCATTGAGTC	293
GNG11	204115_at	0.18	GGGAGAACTGCATCCTAAGTGGAA	294
DDAH1	209094_at	0.18	TATGGTTATCCACTCTGTGTGCCAA	295
CYR61	210764_s_at	0.18	GAAATACCGGCCAAGTACTGCGGT	296
GNG12	212294_at	0.18	GTAATAATGTCTTGTTTTGTAGCCAT	297
TSPAN6	209109_s_at	0.18	ATTTCTTTGGAGTTGCTTGCTTCC	298
LIMCH1	212327_at	0.18	TCCAAAAGCTAGTCCCTACTCTTTA	299
SFN	33323_r_at	0.18	CCATGTTTCTCTCAATAAAGTTCC	300

TABLE 4

Biomarkers of resistance to irifolven. Dashes indicate that the Affymetrix probeset has not been mapped to a specific gene. Affymetrix IDs refer to the array type HG-U133 Plus 2.

Gene	Affymetrix ID	Correlation	Affymetrix Probe Sequence	Affymetrix Probe SEQ ID NO:
IGLC1	214677_x_at	-0.31	AAGTCCCACAGAAGCTACAGCTGCC	301
IGLC1	209138_x_at	-0.29	AAGACAGTGGCCCCCTACAGAATGTT	302
CYAT1 IGLC1 IGLV1-44	215121_x_at	-0.28	GAGCCGTGACAGTGGCCTGGAAGGC	303
LAPTM5	201721_s_at	-0.26	AAAACAGTCCCTTCAAACACACAAT	304
ARHGDIB	201288_at	-0.25	GTCTCCATCTCAGTACACAATCATT	305
IGLV1-44	215379_x_at	-0.25	CTCCTCTGAGGAGCTTCAAGCCAAC	306
SLC43A3	213113_s_at	-0.24	CGAAGCCTATATGTGCCTGGATCCT	307
LCP1	208885_at	-0.24	TAAGCATCCTTAGGGTTCTGCCTCT	308
HCLS1	202957_at	-0.22	CTGTCTACTGCAACTGTGATTTCCT	309
CD53	203416_at	-0.22	AAAGGGCAAGATCTCATTTCATTT	310
ARHGDIB	1555812_a_at	-0.22	CTGTGGTGACAGATCCGAAAGCCCC	311

TABLE 4-continued

Biomarkers of resistance to irifolven. Dashes indicate that the Affymetrix probeset has not been mapped to a specific gene. Affymetrix IDs refer to the array type HG-U133 Plus 2.

Gene	Affymetrix ID	Correlation	Affymetrix Probe Sequence	Affymetrix Probe SEQ ID NO:
SLC43A3	210692_s_at	-0.21	TCATCCTGCAAGTGATCAGCCGCTC	312
MZB1	221286_s_at	-0.21	TAAAACCCAGTGACCTCACTTCTTT	313
RASSF5	223322_at	-0.21	TGCTGCAACCGCTGTGAATGCTGCT	314
FAM46C	226811_at	-0.2	TGTTCTATATTTGCATAGCCTTTGA	315
RCSD1	225763_at	-0.2	CAAAAAGGCCTTATGTCACCACTGG	316
IGJ	212592_at	-0.2	ATAGGTCAATTATATGTCTCCATTA	317
IGLC1 IGLJ3 IGLV2-14 IGLV@	217148_x_at	-0.19	TAATCGGCCCTCAGGGGTTTCTAAT	318
LPXN	216250_s_at	-0.19	TTTCACCTCTAGTGATGGCCCTACT	319
ITGB7	205718_at	-0.19	TGCAAAGAGCGGACCCTGGACAACC	320
GTSF1	227711_at	-0.19	AACTGACAAGCACACTTTTTTCCTC	321
IGLL3P	215946_x_at	-0.19	GTGGCCCTGCAGAATGTTTCATAGG	322
ICAM2	213620_s_at	-0.19	TAGTCACGGTGGTGTCCGGTGTGCT	323
PRSS2	205402_x_at	-0.18	GAGAGCACAAACATCGAAGTCTGGA	324
MZB1	223565_at	-0.18	TACACGATGTCCTGGACCGGAGCTG	325
IFITM1	214022_s_at	-0.18	CAACCTTTGCACTCCACTGTGCAAT	326
IKZF1	227346_at	-0.18	TGCAGTCATATTTCCAGTCTGCCTC	327
CELF2	202157_s_at	-0.18	GTCACCTTTTGCTGAACTCACAGTT	328
RAC2	213603_s_at	-0.18	GCCAGATGGTTGCTGCCACAACCTG	329
IFITM1 IFITM2	201601_x_at	-0.18	ACCCTCTTCTTGAACGGTGTGCTGTC	330
PVALB	205336_at	-0.18	GATGTCGATGACAGACTTGCTGAAC	331
CYFIP2	215785_s_at	-0.18	CAGCCTGCCATAGGATCCAACCTGGA	332
CDK6	224847_at	-0.18	GTGTTTCTGTTGCAGTGGCAAAGGT	333
MYB	204798_at	-0.18	AAGCATGCGTTGCACTTCTTTTTTG	334
TCF4	212386_at	-0.18	GTCTAGTGCTCTTTTGCTATAAAAT	335
CCND2	200953_s_at	-0.17	TATGTTTCATCACCTTATATCATGT	336
PPM1K	235061_at	-0.17	AAGACTCTTAGGCAGCTATGGGTTT	337
LAPTM5	201_720_s_at	-0.17	TGTTCAAGTGCCTGTGGCGGTGCTA	338
CDK6	224851_at	-0.17	GCTTCAGGCAACTTAGCTGTGTACA	339
IFI16	208966_x_at	-0.17	GACATACTCAATCCTGATTCCAAGT	340
IFI16	206332_s_at	-0.17	AGAAAGACATACTCAATCCTGATTC	341
EVI2A	204774_at	-0.17	ACACCAGCTTATCAACCAACACAGC	342
CDK6	224848_at	-0.17	GGGTGCATGTTCTTAAAGGTGCAT	343
CORO1A	209083_at	-0.17	GCTCCAGAAGCGCTTGGACAGGCTG	344
LINC00341 SYNE3	219563_at	-0.17	GAGGGACCATATCTACTCTTGTTCAT	345

TABLE 4-continued

Biomarkers of resistance to irifolven. Dashes indicate that the Affymetrix probeset has not been mapped to a specific gene. Affymetrix IDs refer to the array type HG-U133 Plus 2.

Gene	Affymetrix ID	Correlation	Affymetrix Probe Sequence	Affymetrix Probe SEQ ID NO:
LOC101928620 POU2AF1	205267_at	-0.16	GCAGGTGTGCTTAGCTCTTGATAGT	346
CX3CR1	205898_at	-0.16	GAAAATACCCCATCATTCATGCTAC	347
DOCK2	213160_at	-0.16	GAAGGCAAACAGATCCCAGACTCGC	348
WIPF1	202664_at	-0.16	GGTAGAGACTACCTAGACATCTGC	349
TCF4	213891_s_at	-0.16	AGGTTGTGTGCTGGAGTTCCTTCAA	350
ST3GAL6	210942_s_at	-0.16	ACAGGAATTATTGCCATCACATTGG	351
GLYR1 SEPT6	212414_s_at	-0.16	CAGTGTAGATGGCTCTTGTTTTTGT	352
TRBC1	211796_s_at	-0.16	CAATGACTCCAGATACTGCCTGAGC	353
AZGP1	209309_at	-0.16	AAAAAATCATCTCACCTTGAGCCCA	354
LY96	206584_at	-0.16	ATCTCTATATAACTGTCAACACCAT	355
GIMAP2	232024_at	-0.16	TGTTTTGTTGCTTACTCTTAGTAT	356
HERC5	219863_at	-0.16	ACATCATATTCCTTACCTCTTTTGG	357
IGLL5	217235_x_at	-0.15	GGCTCCAGGCTGAGGATGAGGCTGA	358
ST3GAL6	213355_at	-0.15	GGCTCTGGAAATCTAAGTTCATACT	359
ICAM3	204949_at	-0.15	TGGTACTTATCAGTGCCAAGCGTCC	360
LCP2	205269_at	-0.15	TGTTTTTTACAGCCAAACCTCTGTC	361
NCKAP1L	238668_at	-0.15	GAATAGTTGTCTTTTGAGCCTCAGA	362
P2RY8	229686_at	-0.15	TTGAGTCCGGGTGTTCAAGGGCCAA	363
CCR1	205098_at	-0.15	CCAAGGACCCCTTATTTATCATGCC	364
GMFG	204220_at	-0.15	AGCTGAGGAAATTCGCTTCCGAAA	365
EVI2B	211742_s_at	-0.15	TCCATCCTCAAATGACTCTTTTTTC	366
-	229670_at	-0.15	GTGAAATCAGGGTGCTGTTACCAA	367
BCL2	203685_at	-0.15	GATGGAAAGGCTCGCTCAATCAAGA	368
RAC2	207419_s_at	-0.15	ATCCACAGACGGACGTCTTCCTCAT	369
IQGAP2	203474_at	-0.15	TACTGCCTCATGTAAAGACTCTTGC	370
IFI16	208965_s_at	-0.15	ACTTCATTTTCTTAGCGTTTCTGGA	371
PPM1K	226773_at	-0.15	CTGATGTGTCCCAAACCTGATTTAA	372
LEF1	221558_s_at	-0.15	TGTAACACATAGTGGCTTCTCCGCC	373
SLC1A4	209610_s_at	-0.15	GCTAACCAGTATGTTCTTCTTTTT	374
CD38	205692_s_at	-0.15	CTCCTTGACTCCTTGTGGTTTATGT	375
ALDH1A2 LOC101928635	207016_s_at	-0.15	TGAGCCCTGACAGATGCCGTATTTT	376
SSBP2	203787_at	-0.15	ACATTGACCCACAGGACATTGTAAA	377
PTPRC	212588_at	-0.15	GCATTTAGTCCAATGTCTTTTAAAG	378
ERN1	227755_at	-0.15	AGAAAGCATTACCAGTCACCTACTC	379

TABLE 4-continued

Biomarkers of resistance to irifolven. Dashes indicate that the Affymetrix probeset has not been mapped to a specific gene. Affymetrix IDs refer to the array type HG-U133 Plus 2.

Gene	Affymetrix ID	Correlation	Affymetrix Probe Sequence	Affymetrix Probe SEQ ID NO:
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FAM26F	229390_at	-0.14	ATACGGTGATTCTGTCTTGGCTT	382
IGK IGKC	224795_x_at	-0.14	CTCGCCCGTCACAAAGAGCTTCAAC	383
PTPRC	207238_s_at	-0.14	AATGAGGAAACTCCAAACCTCCTGT	384
TCF4	222146_s_at	-0.14	TATCTTAAACCCACATAAACACTTC	385
RASSF5	1554834_a_at	-0.14	AGCACATTCTTTTGCAGGTCTGAG	386
ARHGAP15 LOC101928361	218870_at	-0.14	ACGTTGTCACCGGAGCACTGAAGAT	387
—	236191_at	-0.14	GGAACACATTAGTCTATGGGACCTT	388
MAF	209348_s_at	-0.14	GTATTTGGGACTGAATTGCACTAAG	389
CD8B LOC100996919	215332_s_at	-0.14	TGTCCCCCTTGTGGAACCAAATGTA	390
ATF3	202672_s_at	-0.14	GAATTCTCCCAGCGTTAACACAAAA	391
CD3D	213539_at	-0.14	TGCTCAGTACAGCCACCTTGAGGA	392
SLC1A4	212811_x_at	-0.14	GTTTTTCATGAAGTAGCAACCCACC	393
IGK IGKC	221651_x_at	-0.14	CTCGCCCGTCACAAAGAGCTTCAAC	394
IGK IGKC	221671_x_at	-0.14	AAATCTGGAAGTGCCTCTGTTGTGT	395
SAMSN1	220330_s_at	-0.14	GTATCTCTAACATTCCAAATTACTG	396
PIM2	204269_at	-0.14	CCCTAGCCTAGGGTCCCATTATGGG	397
DOCK8	225502_at	-0.14	GTAATGGTGGACTAATTGCTGTATA	398
TCF4	203753_at	-0.14	GTGCAACTTGAGGGACGACTTTCTT	399
PTPN7	204852_s_at	-0.14	TCATCCATCTCAGCATCAACACAAT	400

Example 3

Predicting Responsiveness to Irifolven in Various Cancer Patient Populations

An mRNA-based predictor of responsiveness to irifolven developed according to the methods of the invention was applied to 3,522 patients having a variety of cancers. Each patient had a pre-treatment measurement of gene expression with an Affymetrix array. The predicted irifolven sensitivity of each patient was calculated as the difference between the mean of the expression levels of the biomarkers of sensitivity and the mean of the expression levels of the biomarkers of resistance for the patient. When the patients were grouped by cancer types, and cancer types predicted to be more responsive to irifolven were identified (FIG. 1).

Of 27 different cancer types, solid tumor cancers were predicted to be more responsive to irifolven treatment than hematological cancers. In particular, patients with prostate cancer, ovarian cancer, hepatocellular carcinoma (HCC), breast cancer, cervical cancer, renal cell carcinoma (RCC), esophageal cancer, melanoma, glioma, pancreatic cancer, gastrointestinal stromal tumors (GIST), sarcoma, estrogen

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receptor-positive (ERpos) breast cancer, non-small cell lung carcinoma (NSCLC), colon cancer, bladder cancer, and squamous cell carcinoma of the head and neck (SCCHN) were predicted to be more responsive to irifolven treatment. Patients with hematological cancer types were also predicted to be responsive to irifolven treatment, in particular, cutaneous T-cell lymphoma (CTCL), multiple myeloma, acute myelogenous leukemia (AML), acute lympho-blastic leukemia (ALL), chronic lymphocytic leukemia (CLL), myelodysplastic syndrome (MDS), chronic myelogenous leukemia-chronic phase (CMLCP), diffuse large B-cell lymphoma (DLBCL), peripheral T-cell lymphoma (PTCL), and Hodgkin's lymphoma patients were predicted to be the most responsive to irifolven.

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The median of the boxplots shown in FIG. 1 is a cutoff that may be used to separate patients predicted to be responsive to irifolven treatment from patients predicted to be non-responsive to irifolven treatment for a given cancer type. Values above the median indicate patients predicted to be responsive to irifolven, while values below the median indicate patients predicted to be non-responsive to irifolven. For a test sample from an individual patient, it is useful to

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compare the test sample to the reference population for the same cancer type. If the test sample is above the median for the reference population of the same cancer type, then the patient is predicted to be responsive to irifolven treatment. If the test sample is below the median for the reference population of the same cancer type, then the patient is predicted to be non-responsive to irifolven treatment. This method for predicting patient responsiveness can also be used when the reference cancer population consists of only two patients: a patient responsive to irifolven treatment and a patient non-responsive to irifolven treatment.

Example 4

Predicting Responsiveness of Prostate Cancer Patients to Irifolven

The diagnostic methods of the present invention can be used to predict the responsiveness of a prostate cancer patient to treatment with irifolven. In particular, the prostate cancer patient may be one that has not previously received any cancer treatment or one that has received a cancer treatment other than irifolven. Moreover, the patient may be one diagnosed with prostate cancer or one with recurrence of prostate cancer. The patient may also have prostate cancer that is resistant to treatment, such as treatment with docetaxel, cabazitaxel, mitoxantrone, estramustine, prednisone, and/or surgery.

A biological sample (e.g., a prostate tissue sample) may be obtained from the patient through methods well known in the art. The sample may be frozen and/or prepared, e.g., by formalin fixation and paraffin embedding. In particular, mRNA can be isolated from the sample and a gene expression profile can be determined, e.g., using a microarray platform, such as the Affymetrix HG-U133A or HG-U133_Plus_2 array, for one or more of the biomarkers shown in Tables 1-4. One or more of the biomarkers shown in Tables 1-4 can also be measured, e.g., by sequencing or PCR-based techniques, such as those described herein.

For example, the expression level of one or more biomarkers of sensitivity to irifolven can be determined in the sample from the patient, such as one or more of ATP1B1 (SEQ ID NO: 201 or 219), UCHL1 (SEQ ID NO: 202), PTGR1 (SEQ ID NO: 203 or 210), NME7 (SEQ ID NO: 204), PLS3 (SEQ ID NO: 205), S100A10 (SEQ ID NO: 206), CD24 (SEQ ID NO: 207, 209, or 220), NQO1 (SEQ ID NO: 208 or 216), MYOF (SEQ ID NO: 211), LAPTM4B (SEQ ID NO: 212), CALD1 (SEQ ID NO: 213), PDGFC (SEQ ID NO: 214), BASP1 (SEQ ID NO: 215), ID1 (SEQ ID NO: 217), and GJA1 (SEQ ID NO: 218). In particular, the biomarker is ATP1B1 (SEQ ID NO: 201). The expression level of one or more biomarkers of resistance to irifolven can also be determined in the sample from the patient, such as one or more of IGLC1 (SEQ ID NO: 301, 302, 303, or 318), LAPTM5 (SEQ ID NO: 304 or 338), ARHGDIB (SEQ ID NO: 305 or 311), SLC43A3 (SEQ ID NO: 307), LCP1 (SEQ ID NO: 308), HCLS1 (SEQ ID NO: 309), CD53 (SEQ ID NO: 310), MZB1 (SEQ ID NO: 313), RASSF5 (SEQ ID NO: 314 or 386), FAM46C (SEQ ID NO: 315), RCSD1 (SEQ ID NO: 316), IGJ (SEQ ID NO: 317), LPXN (SEQ ID NO: 319), ITGB7 (SEQ ID NO: 320), and GTSF1 (SEQ ID NO: 321). In particular, the biomarker is IGLC1 (SEQ ID NO: 301, 302, 303, or 318).

The prostate cancer patient may be responsive to irifolven if the expression level of one or more of the biomarkers of sensitivity is substantially similar to the expression level of the biomarkers of sensitivity in a cell or tissue known to be sensitive to irifolven. The prostate cancer patient may

also be responsive to irifolven if the expression level of one or more of the biomarkers of resistance is substantially dissimilar to the expression level of the biomarkers of resistance in a cell or tissue known to be resistant to irifolven. If the patient is predicted to be responsive, then the patient can be administered irifolven, such as irifolven administered intravenously at a dose of about 0.05 mg/kg to 5 mg/kg (e.g., about 0.1 mg/kg to 1 mg/kg, such as about 0.45 mg/kg). Conversely, if the patient is predicted to be non-responsive to irifolven treatment, then the patient can be administered one or more therapies other than irifolven, such as radiation or a therapeutic agent (e.g., docetaxel, cabazitaxel, mitoxantrone, estramustine, prednisone, and/or another therapeutic agent described herein).

Example 5

Predicting Responsiveness of Ovarian Cancer Patients to Irifolven

The diagnostic methods of the present invention can be used to predict the responsiveness of an ovarian cancer patient to treatment with irifolven. In particular, the ovarian cancer patient may be one that has not previously received any cancer treatment or one that has received a cancer treatment other than irifolven. Moreover, the patient may be one diagnosed with ovarian cancer or one with recurrence of ovarian cancer. The patient may also have ovarian cancer that is resistant to treatment, such as treatment with docetaxel, carboplatin, bevacizumab, paclitaxel, gemcitabine, doxorubicin, topotecan, etoposide, tamoxifen, and/or letrozole.

A biological sample (e.g., an ovarian tissue sample) may be obtained from the patient through methods well known in the art. The sample may be frozen and/or prepared, e.g., by formalin fixation and paraffin embedding. In particular, mRNA can be isolated from the sample and a gene expression profile can be determined, e.g., using a microarray platform, such as the Affymetrix HG-U133A or HG-U133_Plus_2 array, for one or more of the biomarkers shown in Tables 1-4. One or more of the biomarkers shown in Tables 1-4 can also be measured, e.g., by sequencing or PCR-based techniques, such as those described herein.

For example, the expression level of one or more biomarkers of sensitivity to irifolven can be determined in the sample from the patient, such as one or more of ATP1B1 (SEQ ID NO: 201 or 219), UCHL1 (SEQ ID NO: 202), PTGR1 (SEQ ID NO: 203 or 210), NME7 (SEQ ID NO: 204), PLS3 (SEQ ID NO: 205), S100A10 (SEQ ID NO: 206), CD24 (SEQ ID NO: 207, 209, or 220), NQO1 (SEQ ID NO: 208 or 216), MYOF (SEQ ID NO: 211), LAPTM4B (SEQ ID NO: 212), CALD1 (SEQ ID NO: 213), PDGFC (SEQ ID NO: 214), BASP1 (SEQ ID NO: 215), ID1 (SEQ ID NO: 217), and GJA1 (SEQ ID NO: 218). In particular, the biomarker is ATP1B1 (SEQ ID NO: 201). The expression level of one or more biomarkers of resistance to irifolven can also be determined in the sample from the patient, such as one or more of IGLC1 (SEQ ID NO: 301, 302, 303, or 318), LAPTM5 (SEQ ID NO: 304 or 338), ARHGDIB (SEQ ID NO: 305 or 311), SLC43A3 (SEQ ID NO: 307), LCP1 (SEQ ID NO: 308), HCLS1 (SEQ ID NO: 309), CD53 (SEQ ID NO: 310), MZB1 (SEQ ID NO: 313), RASSF5 (SEQ ID NO: 314 or 386), FAM46C (SEQ ID NO: 315), RCSD1 (SEQ ID NO: 316), IGJ (SEQ ID NO: 317), LPXN (SEQ ID NO: 319), ITGB7 (SEQ ID NO: 320), and GTSF1 (SEQ ID NO: 321). In particular, the biomarker is IGLC1 (SEQ ID NO: 301, 302, 303, or 318).

The ovarian cancer patient may be responsive to irifolven if the expression level of one or more of the biomarkers of sensitivity is substantially similar to the expression level of the biomarkers of sensitivity in a cell or tissue known to be sensitive to irifolven. The ovarian cancer patient may also be responsive to irifolven if the expression level of one or more of the biomarkers of resistance is substantially dissimilar to the expression level of the biomarkers of resistance in a cell or tissue known to be resistant to irifolven. If the patient is predicted to be responsive, then the patient can be administered irifolven, such as irifolven administered intravenously at a dose of about 0.05 mg/kg to 5 mg/kg (e.g., about 0.1 mg/kg to 1 mg/kg, such as about 0.45 mg/kg). Conversely, if the patient is predicted to be non-responsive to irifolven treatment, then the patient can be administered one or more therapies other than irifolven, such as radiation or a therapeutic agent (e.g., docetaxel, carboplatin, bevacizumab, paclitaxel, gemcitabine, doxorubicin, topotecan, etoposide, tamoxifen, letrozole, and/or another therapeutic agent described herein).

Example 6

Predicting Responsiveness of Hepatocellular Carcinoma (HCC) Patients to Irifolven

The diagnostic methods of the present invention can be used to predict the responsiveness of a hepatocellular carcinoma (HCC) patient to treatment with irifolven. In particular, the HCC patient may be one that has not previously received any cancer treatment or one that has received a cancer treatment other than irifolven. Moreover, the patient may be one diagnosed with HCC or one with recurrence of HCC. The patient may also have HCC that is resistant to treatment, such as treatment with sorafenib, doxorubicin, cisplatin, fluorouracil, gemcitabine, capecitabine, oxaliplatin, interferon-alpha, and/or 5-fluorouracil (5-FU).

A biological sample (e.g., a liver tissue sample) may be obtained from the patient through methods well known in the art. The sample may be frozen and/or prepared, e.g., by formalin fixation and paraffin embedding. In particular, mRNA can be isolated from the sample and a gene expression profile can be determined, e.g., using a microarray platform, such as the Affymetrix HG-U133A or HG-U133_Plus_2 array, for one or more of the biomarkers shown in Tables 1-4. One or more of the biomarkers shown in Tables 1-4 can also be measured, e.g., by sequencing or PCR-based techniques, such as those described herein.

For example, the expression level of one or more biomarkers of sensitivity to irifolven can be determined in the sample from the patient, such as one or more of ATP1B1 (SEQ ID NO: 201 or 219), UCHL1 (SEQ ID NO: 202), PTGR1 (SEQ ID NO: 203 or 210), NME7 (SEQ ID NO: 204), PLS3 (SEQ ID NO: 205), S100A10 (SEQ ID NO: 206), CD24 (SEQ ID NO: 207, 209, or 220), NQO1 (SEQ ID NO: 208 or 216), MYOF (SEQ ID NO: 211), LAPTM4B

(SEQ ID NO: 212), CALD1 (SEQ ID NO: 213), PDGFC (SEQ ID NO: 214), BASP1 (SEQ ID NO: 215), ID1 (SEQ ID NO: 217), and GJA1 (SEQ ID NO: 218). In particular, the biomarker is ATP1B1 (SEQ ID NO: 201). The expression level of one or more biomarkers of resistance to irifolven can also be determined in the sample from the patient, such as one or more of IGLC1 (SEQ ID NO: 301, 302, 303, or 318), LAPTM5 (SEQ ID NO: 304 or 338), ARHGDIB (SEQ ID NO: 305 or 311), SLC43A3 (SEQ ID NO: 307), LCP1 (SEQ ID NO: 308), HCLS1 (SEQ ID NO: 309), CD53 (SEQ ID NO: 310), MZB1 (SEQ ID NO: 313), RASSF5 (SEQ ID NO: 314 or 386), FAM46C (SEQ ID NO: 315), RCSD1 (SEQ ID NO: 316), IGJ (SEQ ID NO: 317), LPXN (SEQ ID NO: 319), ITGB7 (SEQ ID NO: 320), and GTSF1 (SEQ ID NO: 321). In particular, the biomarker is IGLC1 (SEQ ID NO: 301, 302, 303, or 318).

The HCC patient may be responsive to irifolven if the expression level of one or more of the biomarkers of sensitivity is substantially similar to the expression level of the biomarkers of sensitivity in a cell or tissue known to be sensitive to irifolven. The HCC patient may also be responsive to irifolven if the expression level of one or more of the biomarkers of resistance is substantially dissimilar to the expression level of the biomarkers of resistance in a cell or tissue known to be resistant to irifolven. If the patient is predicted to be responsive, then the patient can be administered irifolven, such as irifolven administered intravenously at a dose of about 0.05 mg/kg to 5 mg/kg (e.g., about 0.1 mg/kg to 1 mg/kg, such as about 0.45 mg/kg). Conversely, if the patient is predicted to be non-responsive to irifolven treatment, then the patient can be administered one or more therapies other than irifolven, such as radiation or a therapeutic agent (e.g., docetaxel, carboplatin, bevacizumab, paclitaxel, gemcitabine, doxorubicin, topotecan, etoposide, tamoxifen, letrozole, and/or another therapeutic agent described herein).

OTHER EMBODIMENTS

All publications, patents, and patent applications mentioned in the above specification are hereby incorporated by reference. Various modifications and variations of the described device and methods of use of the invention will be apparent to those skilled in the art without departing from the scope and spirit of the invention. Although the invention has been described in connection with specific embodiments, it should be understood that the invention as claimed should not be unduly limited to such specific embodiments. Indeed, various modifications of the described modes for carrying out the invention that are obvious to those skilled in the art are intended to be within the scope of the invention. For example, it is anticipated that measuring the level of proteins, metabolites, identifying genetic mutations and DNA copy number variations, all will be useful in determining patient responsiveness.

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The invention claimed is:

1. A method of determining irofulven sensitivity in a 40 patient by detecting expression of a biomarker in the patient with a cancer that is resistant to one or more cancer therapies other than irofulven comprising:

- (a) isolating nucleic acid molecules obtained from a 45 sample from the patient: and
- (b) measuring in the sample:
 - i) the level of expression of one or more biomarkers of irofulven sensitivity selected from the biomarkers of Tables 1 and 3; and/or
 - ii) the level of expression of one or more biomarkers of 50 irofulven resistance selected from the biomarkers of Tables 2 and 4; and
- (c) determining irofulven sensitivity in the patient based on the level of expression of the one or more biomarkers of irofulven sensitivity and/or the one or more 55 biomarkers of irofulven resistance.

2. A method of determining responsiveness of a cancer in a patient having cancer to irofulven comprising:

- (a) contacting one or more nucleic acid molecules 60 obtained from a sample from the patient with a device comprising:
 - i) one or more single-stranded nucleic acid molecules capable of specifically hybridizing with the nucleotides of one or more biomarkers of irofulven sensitivity selected from the biomarkers of Tables 1 and 3; and/or
 - ii) one or more single-stranded nucleic acid molecules 65 capable of specifically hybridizing with the nucleotides of one or more biomarkers of irofulven resistance selected from the biomarkers of Tables 2 and 4;
- (b) measuring hybridization, or an amplification product resulting from hybridization, between the one or more nucleic acid molecules from the patient and the single-stranded nucleic acid molecules of the device to detect a level of expression of one or more of the biomarkers of irofulven sensitivity and/or one or more of the biomarkers of irofulven resistance; and
- (c) determining irofulven sensitivity in the patient based on the level of expression of the one or more biomarkers of irofulven sensitivity and/or the one or more biomarkers of irofulven resistance.

3. The method of claim 1, wherein one or more of the cancer therapies comprises surgery, radiation, or a therapeutic agent.

4. The method of claim 2, wherein the patient is resistant to one or more cancer therapies other than irofulven, wherein one or more of the cancer therapies comprises surgery, radiation, or a therapeutic agent.

5. The method of claim 1, wherein the biomarker of sensitivity is selected from one or more of ATP1B1 (SEQ ID NO: 201 or 219), UCHL1 (SEQ ID NO: 202), PTGR1 (SEQ ID NO: 203 or 210), NME7 (SEQ ID NO: 204), PLS3 (SEQ ID NO: 205), S100A10 (SEQ ID NO: 206), CD24 (SEQ ID NO: 207, 209, or 220), NQO1 (SEQ ID NO: 208 or 216),

MYOF (SEQ ID NO: 211), LAPTM4B (SEQ ID NO: 212), CALD1 (SEQ ID NO: 213), PDGFC (SEQ ID NO: 214), BASP1 (SEQ ID NO: 215), ID1 (SEQ ID NO: 217), and GJA1 (SEQ ID NO: 218) and/or the biomarker of resistance is selected from one or more of IGLC1 (SEQ ID NO: 301, 302, 303, or 318), LAPTM5 (SEQ ID NO: 304 or 338), ARHGDIB (SEQ ID NO: 305 or 311), SLC43A3 (SEQ ID NO: 307), LCP1 (SEQ ID NO: 308), HCLS1 (SEQ ID NO: 309), CD53 (SEQ ID NO: 310), MZB1 (SEQ ID NO: 313), RASSF5 (SEQ ID NO: 314 or 386), FAM46C (SEQ ID NO: 315), RCSD1 (SEQ ID NO: 316), IGJ (SEQ ID NO: 317), LPXN (SEQ ID NO: 319), ITGB7 (SEQ ID NO: 320), and GTSF1 (SEQ ID NO: 321).

6. The method of claim 2, wherein the biomarker of sensitivity is selected from one or more of ATP1B1 (SEQ ID NO: 201 or 219), UCHL1 (SEQ ID NO: 202), PTGR1 (SEQ ID NO: 203 or 210), NME7 (SEQ ID NO: 204), PLS3 (SEQ ID NO: 205), S100A10 (SEQ ID NO: 206), CD24 (SEQ ID NO: 207, 209, or 220), NQO1 (SEQ ID NO: 208 or 216), MYOF (SEQ ID NO: 211), LAPTM4B (SEQ ID NO: 212), CALD1 (SEQ ID NO: 213), PDGFC (SEQ ID NO: 214), BASP1 (SEQ ID NO: 215), ID1 (SEQ ID NO: 217), and GJA1 (SEQ ID NO: 218) and/or the biomarker of resistance is selected from one or more of IGLC1 (SEQ ID NO: 301, 302, 303, or 318), LAPTM5 (SEQ ID NO: 304 or 338), ARHGDIB (SEQ ID NO: 305 or 311), SLC43A3 (SEQ ID NO: 307), LCP1 (SEQ ID NO: 308), HCLS1 (SEQ ID NO: 309), CD53 (SEQ ID NO: 310), MZB1 (SEQ ID NO: 313), RASSF5 (SEQ ID NO: 314 or 386), FAM46C (SEQ ID NO: 315), RCSD1 (SEQ ID NO: 316), IGJ (SEQ ID NO: 317), LPXN (SEQ ID NO: 319), ITGB7 (SEQ ID NO: 320), and GTSF1 (SEQ ID NO: 321).

7. The method of claim 1, wherein the method is performed using a device.

8. The method of claim 2, wherein the device is a microarray.

9. The method of claim 1, wherein the method comprises performing an assay selected from the group consisting of microarray, quantitative reverse transcriptase polymerase chain reaction (qRT-PCR), RNA-seq, and Nanostring analysis.

10. The method of claim 2, wherein the method comprises performing an assay selected from the group consisting of microarray, quantitative reverse transcriptase polymerase chain reaction (qRT-PCR), RNA-seq, and Nanostring analysis.

11. The method of claim 1, wherein the level of expression of one or more of the biomarkers of sensitivity and/or one or more of the biomarkers of resistance is determined by detecting the level of mRNA transcribed from one or more genes encoding one or more of the biomarkers of Tables 1-4.

12. The method of claim 2, wherein the level of expression of one or more of the biomarkers of sensitivity and/or one or more of the biomarkers of resistance is determined by detecting the level of mRNA transcribed from one or more genes encoding one or more of the biomarkers of Tables 1-4.

13. The method of claim 1, wherein the cancer is selected from a solid tumor cancer and a hematological cancer and/or wherein the cancer is selected from the group consisting of prostate cancer, ovarian cancer, hepatocellular carcinoma

(HCC), cervical cancer, renal cell carcinoma (RCC), esophageal cancer, melanoma, glioma, pancreatic cancer, gastrointestinal stromal tumors (GIST), sarcoma, estrogen receptor-positive (ERpos) breast cancer, non-small cell lung carcinoma (NSCLC), colon cancer, bladder cancer, squamous cell carcinoma of the head and neck (SCCHN), acute myelogenous leukemia (AML), acute lympho-blastic leukemia (ALL), chronic lymphocytic leukemia (CLL), myelodysplastic syndrome (MDS), chronic myelogenous leukemia—chronic phase (CMLCP), diffuse large B-cell lymphoma (DLBCL), cutaneous T-cell lymphoma (CTCL), peripheral T-cell lymphoma (PTCL), and Hodgkin's lymphoma.

14. The method of claim 2, wherein the cancer is selected from a solid tumor cancer and a hematological cancer and/or wherein the cancer is selected from the group consisting of prostate cancer, ovarian cancer, hepatocellular carcinoma (HCC), cervical cancer, renal cell carcinoma (RCC), esophageal cancer, melanoma, glioma, pancreatic cancer, gastrointestinal stromal tumors (GIST), sarcoma, estrogen receptor-positive (ERpos) breast cancer, non-small cell lung carcinoma (NSCLC), colon cancer, bladder cancer, squamous cell carcinoma of the head and neck (SCCHN), acute myelogenous leukemia (AML), acute lympho-blastic leukemia (ALL), chronic lymphocytic leukemia (CLL), myelodysplastic syndrome (MDS), chronic myelogenous leukemia—chronic phase (CMLCP), diffuse large B-cell lymphoma (DLBCL), cutaneous T-cell lymphoma (CTCL), peripheral T-cell lymphoma (PTCL), and Hodgkin's lymphoma.

15. The method of claim 1, wherein: (a) the sample from the patient is a tumor sample; (b) the patient exhibits cancer relapse after treatment with a therapeutic agent other than irifolven; (c) the patient exhibits cancer relapse prior to treatment with irifolven; or (d) the patient has not been administered a treatment for cancer.

16. The method of claim 2, wherein: (a) the sample from the patient is a tumor sample; (b) the patient exhibits cancer relapse after treatment with a therapeutic agent other than irifolven; (c) the patient exhibits cancer relapse prior to treatment with irifolven; or (d) the patient has not been administered a treatment for cancer.

17. The method of claim 1, wherein the biomarker of sensitivity is ATP1B1 (SEQ ID NO: 201 or 219) and/or the biomarker of resistance is IGLC1 (SEQ ID NO: 301, 302, 303, or 318).

18. The method of claim 17, wherein the biomarker of sensitivity is ATP1B1 (SEQ ID NO: 201 or 219) and the biomarker of resistance is IGLC1 (SEQ ID NO: 301, 302, 303, or 318).

19. The method of claim 2, wherein the biomarker of sensitivity is ATP1B1 (SEQ ID NO: 201 or 219) and/or the biomarker of resistance is IGLC1 (SEQ ID NO: 301, 302, 303, or 318).

20. The method of claim 19, wherein the biomarker of sensitivity is ATP1B1 (SEQ ID NO: 201 or 219) and the biomarker of resistance is IGLC1 (SEQ ID NO: 301, 302, 303, or 318).